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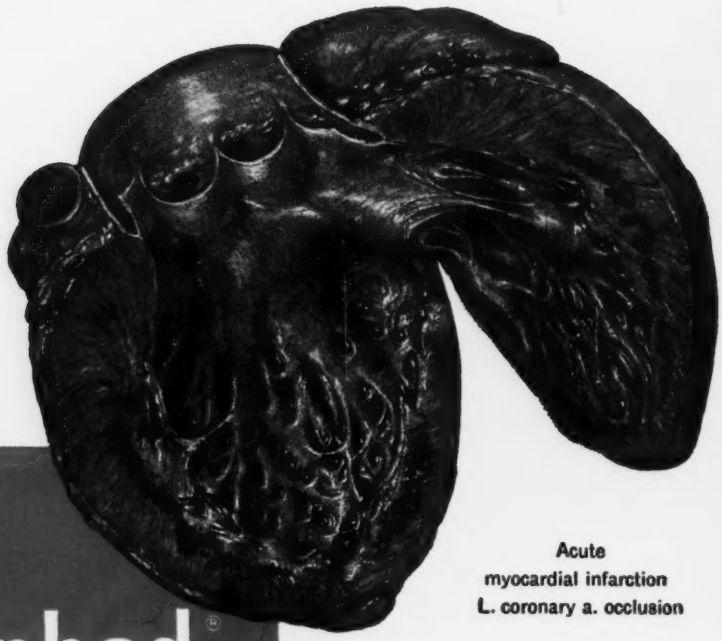

Acute
myocardial infarction
L. coronary a. occlusion

..... may be life-saving

A series of 14 cases of severe shock accompanying myocardial infarction was treated by various methods. All of the 6 patients who received Levophed recovered despite the presence of congestive heart failure.[1]

Write for detailed literature.

The practically instant pressor effect of Levophed—within 10 to 30 seconds—may usually be maintained at desired levels almost indefinitely.

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1. Gazes, P. C., Goldberg, L. I., and Darby, T. D.: *Circulation*, 8: 883, Dec., 1953.

Levophed bitartrate, brand of levarterenol bitartrate

Circulation

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OFFICIAL JOURNAL of the AMERICAN HEART ASSOCIATION

The Heart Muscle and the Electrocardiogram in Coronary Disease

III. A New Classification of Ventricular Myocardial Damage Derived from the Clinicopathologic Findings in 100 Patients

By JOHN J. SAŸEN, M.D., WARNER F. SHELDON, M.D. AND CHARLES C. WOLFERTH, M.D.

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NOTE: *In view of the length of this article, it will be published in two issues. This issue will contain the Introduction, Methods and Results, while the Discussion and References will be published in October, 1955.*—ED.

Methods, designed to study in detail the lesions resulting from coronary disease and to reconstruct accurately the form of all ventricular muscle lesions, have been applied to 100 consecutive electrocardiographed patients who were found to have at least one severe coronary narrowing. Reclassification of lesions into four categories was found necessary to deal with the patterns of damage disclosed. This approach permits conclusions regarding evolution of muscle damage, relationships of arterial obstruction to muscle damage distribution, and the significance of ischemia which would have been impossible otherwise. The value of the new classification for electrocardiography will be discussed in a subsequent section of the report.

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THE INVESTIGATION reported in the series of which this is part III was originally aimed at correlating coronary disease patients' electrocardiographic patterns and myocardial damage found at necropsy. We studied some 250 hearts by a serial slice technic that permits systematic gross and microscopic scrutiny of the ventricular myocardium and the major coronary vessels. Our technic and the electrocardiographic and pathologic findings of the first 150 cases were outlined in 1947 in a preliminary report.[1] In it we emphasized the frequency of multiple lesions and the virtual limitation of myocardial damage to the left ventricular walls and the septum, especially the layers near the left ventricular cavity. We also called attention to the efficiency of electrocardiography in diagnosis and localization of massive damage in the anterior wall, apex and posteroseptal regions of the left ventricle, as well as other anterior lesions that produced breaks in the precordial lead pattern. The limitations of electrocardiography with respect to other areas were noted as was its frequent failure, even when performing most brilliantly, to reflect more than a fraction of the damage actually present.

Part I of our series[2] dealt with the general problem of collecting data for clinicopathologic studies of coronary disease. We discussed some of the inconsistencies and confusion in the literature which have resulted from the mistakes to which autopsy studies, not aimed primarily at study of the ventricular muscle, are liable such as the complete overlooking of some lesions, misinterpretations of their age so that acute damage and healed scar were confused and incorrect determination of their position and anatomic relationships. We also pointed out that these common errors were not random but occurred because some types or positions of damage are much harder to recognize than others, with the serious consequence that the size of a clinicopathologic series was by no means necessarily a protection against progressive distortion of data.

To secure more complete, reliable data we modified methods in general use as follows: (1) serial slice exploration of the ventricular muscle and epicardial coronary arteries; (2) microscopic study of carefully located and oriented blocks of tissue taken from all gross lesions; and (3) following up all the implications of the clinical, electrocardiographic and coronary artery data, in order to suspect or discern very recent damage, evaluate ischemic states not necessarily causing histologic changes, and analyze complex, multiple lesions.[2] We abandoned injection studies of the coronary vessels except in special cases, because histologic detail was sometimes disturbed by perfusion solutions and delayed fixation, which could prevent recognition of the presence of very recent muscle necrosis.

In part II[3] we discussed the difficulties in describing infarcts, scars and coronary lesions; and also the disadvantages of the conventional methods of illustration. A solution of the problem for individual cases was achieved by (a) accurate drawing of the serial slices with the relevant pathologic data in place, and (b) *representation* of arterial and muscle lesions and their important interrelationships by myocardial maps of their locations and dimensions. Since the important muscle lesions of human coronary disease are largely confined to the heavy circular ring of left ventricular and septal muscle, especially the layers nearest the left ventricular cavity, our maps were confined to this area, which furnished the additional advantage of permitting concentration of all relevant pathologic data in a single diagram.

Now, in part III, we report studies of 100 consecutive patients selected from the larger series because each had (1) at least *one significant coronary narrowing*, that is, diminution of the lumen of a major branch to 1 mm. or less at some point; and (2) a recent *electrocardiogram*, including multiple precordial leads. A fundamental problem appeared to be determining the value of electrocardiography for ascertaining the total ventricular myocardial situation. Because, as our earlier studies[1, 6] had suggested, the tracings at best could give us only parts of a patient's picture, we realized that our search for types of total pictures could not be started from the electrocardiographic viewpoint. "To what extent is it possible to

correlate the electrocardiographic pattern of patients suspected of having coronary disease with myocardial damage demonstrable at the autopsy?" we had asked in part I.[2] This question, therefore, had to be approached from the clinicopathologic side.

In short, we decided to see if our data could answer the following questions which must occur to any physician confronted by a patient with myocardial infarction: Is this infarct large or small? What is the condition of the rest of the heart? How much old scarring is there? How much muscle is potentially ischemic and in danger from minor circulatory stress? The two latter questions are of course equally cogent for patients with anginal syndromes or for anyone suspected of having obstructive coronary disease. The attempt to answer all these questions is tantamount to surveying the total ventricular myocardial situation for any particular patient. Concentration upon the coronary lesions themselves cannot answer these questions since the consequence of any given coronary lesion can be determined only by study of the muscle itself.

Our myocardial maps plainly displayed the answers to the questions about infarction and scarring. The ischemic areas were another matter. Estimation of their extent by considering all the coronary and muscle lesions in relation to the clinical and electrocardiographic picture could only be crude, in the present state of our knowledge (see Discussion). When we tried to describe and compare the muscle findings for *groups* of hearts we were checked by a major semantic difficulty. For patients with coronary disease, conventional terminology altogether ignores describing total ventricular myocardial situations, but is concerned rather with certain limited aspects of particular cases—such as, *syndromes* (angina, coronary insufficiency), *focal pathologic changes* (infarction, scar, coronary narrowing or thrombosis), or *"localized" lesions* ("anterior," "lateral," or "posterior" damage) for the purposes of electrocardiographic diagnosis. So, in order to define, describe and derive conclusions about what our maps were showing us,[7] we were obliged to create a vocabulary. We had to consider not only the age, massiveness and full extent of muscle damage, but also to compare the shapes of lesions with the coronary arterial anatomy. From our specimens the original distributions of the three major arterial trunks, left anterior descending, left circumflex and right coronary (see Methods), had been estimated and were indicated on our maps. When we surveyed the series of patients (only two lacked any muscle damage) in terms of both myocardial damage and original coronary arterial distribution, we found they could be divided into two groups of about equal size: those in which damage could be considered restricted to one of the three major coronary regions, and those in which two or all three regions were involved. For a terminology applicable to the whole series of patients we distinguished "regional damage," that is, damage clearly within the original distribution of a single major coronary trunk, from lesions necessarily of greater extent. The latter we called *"widespread* damage." This category includes multiple, separate lesions or continuous sheets of damage reaching well into two or all three coronary regions.*

This paper will begin by describing our procedures, including a simple method of charting whereby groups of hearts of any size may be compared with respect to the age, massiveness and extent of lesions and their relationship to the original coronary artery distributions. It enables us to present the data from 100 patients succinctly. This method clearly shows, not only the pathologic anatomy of a segment of human coronary disease, but also the characteristics of the small number of groups, basically different from one another, to which all our patients with myocardial damage could be assigned. The terminology, notation and classification based on this approach permit great simplifications in the description of data, which will make their presentation easier in subsequent parts of our reports, especially the electrocardiographic section[4] for which this communication will serve as a partial atlas.

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* In our initial classification[7] we used "localized" instead of "regional." Later it became evident that both regional and widespread lesions are *localized* in the strict sense of the word (see Discussion).

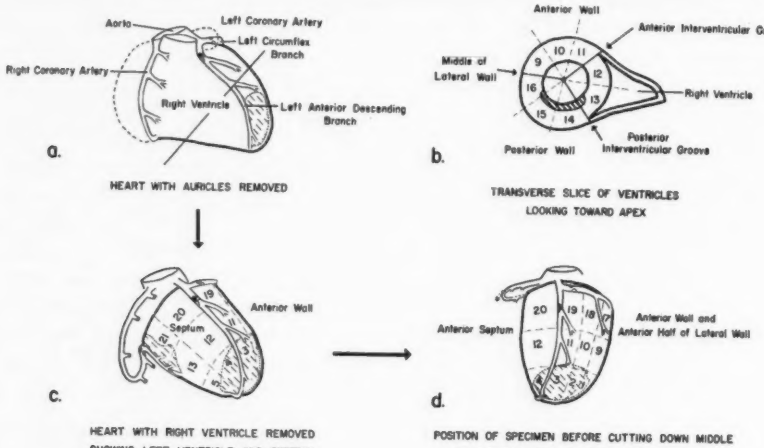

FIG. 1. Hypothetical dissection showing the cardiac anatomy involved in construction of myocardial maps. (*a*) Heart with atria removed, showing the origins of the three coronary "arteries". A diagonal line indicates the plane of a typical slice, perpendicular to the long axis of the left ventricle. The position of two coronary lesions and an apical scar is indicated.

(*b*) Cross-section of the human heart at the level indicated in (*a*) looking down at the apical portion. The similarity in curvature and thickness of the "free" left ventricular walls and their continuation in the septum is shown. The position of anterior and posterior interventricular grooves can readily be seen. Radii have been drawn from the center of the left ventricular cavity. A third radius has been drawn through the center of the lateral wall, opposite the middle of the septum. The drawing will be limited to the left ventricle and septum. The lower edge of a posteroseptal subendocardial scar is shown (lined area).

(*c*) View of the heart illustrated in (*a*) after the right ventricle has been cut away along its attachments at the anterior and posterior interventricular grooves. The coronary vessels have been left in situ to illustrate the course of the right coronary artery supplying the posteroseptal region of the left ventricle. The extension of the left anterior descending branch of the left coronary artery to the back of the apex is also shown. The anterior subendocardial scar and septal portion of the posteroseptal scar are visible, as well as a severe narrowing in the distal right coronary artery. The numbered subdivisions of the myocardium are described in figure 2*b*.

(*d*) The same specimen as in (*c*), turned so that the apex is downward, and rotated so that its edges are formed by the midportions of the septum and the lateral left ventricular wall. If the specimen be cut longitudinally down this mid-lateral wall from base to apex it can be opened like a book and the inside of the left ventricular cavity revealed as in (*e*).

(*e*) View from the left ventricular side of the opened left ventricular and septal muscle mass. The positions of the anterior descending and the posterior interventricular sulcus coronary branches are shown by dotted lines which thus establish the position of the interventricular grooves. The full extent of the two muscle lesions can now be seen. If cuts be made along grooves from apex to base, the specimen will be divided into three segments. Isometric projection drawings of these segments, after they have been placed with the long axis parallel and the basal portions at the same level, form a useful map of the left ventricular and septal myocardium as illustrated in figure 2.

Methods

The criteria for selection of cases have been noted. In the evaluation of each heart there were three stages of procedure: (1) dissection, and recording of all relevant data; (2) representation in a single diagram of the ventricular myocardial situation for each heart; and (3) for the present paper, charting together *groups* of hearts showing broad similarities in type or distribution of muscle damage.

1. *Dissection and Recording*

(a) The epicardial coronary arteries were explored by multiple cross-sectioning at 2 to 3 mm. intervals. This served both to locate all lesions and to determine the caliber and anatomic extent of the various branches. (b) From the results of the coronary artery exploration estimates were made, for later reference, of the *original* configuration of the three major coronary regions. (c) The ventricles were fixed in formalin for 24 to 48 hours and then sections (usually 10) were serially cut in planes perpendicular to the long axis of the left ventricle (figs. 1*a*, *b*). (d) Blocks for microscopic study were taken from all coronary and myocardial lesions and from muscle areas under suspicion because of narrowing of their regional arteries. (e) Drawings were made of all slices to record their shape, the configuration of gross lesions and the sites of microscopic sections. (f) When all histological data were available, the history and electrocardiographic findings were reconsidered in relation to the anatomic picture. Usually additional questions arose necessitating further microscopic blocks or special staining of those already taken. Once the data were brought to this point, our basic record for each case could be considered complete.

2. *Representation of Individual Case Data*

(a) A myocardial map was constructed for the individual heart, account being taken of the actual number of ventricular slices and the gross coronary artery anatomy, as illustrated in figure 2*a*. (b) The maps showed the same landmarks as the serial slices: the interventricular grooves, the mid-lateral wall and the levels of the slices themselves. Consequently the muscle lesions could be transferred accurately slice by slice to the map. Ordinarily only the left ventricle and septum were illustrated, although the right ventricle can be dealt with similarly if desired. (c) The maps were then subdivided into thirds from apex to base, as shown in figure 2*a*, irrespective of the actual number of slices, which varied somewhat with the size of the heart. These lines of "latitude" were helpful in comparing hearts. They correspond to conventional terminology, e.g. "apical," "middle" and "basal" thirds of the heart. It was also helpful to subdivide the anterolateral and posterolateral segments of the maps into thirds and the septal segment in half by subsidiary lines of "longitude". Thus we had 24 areas comprising the left ventricular and septal myocardium. (d) Special features of particular hearts could also be depicted, such as localized thinning of the wall, position of mural thrombi, and the character of papillary muscle lesions.

3. *A System of Notation for Comparing Hearts in Groups*

(a) It proved useful to designate certain of the 24 left ventricular and septal myocardial areas as "central" in each coronary region for all hearts. We tried to select those least subject to the effects of anatomic variations.* These "central" areas, shown by heavy outlines on the map in figure 2*b*, consist of areas 2, 3 and 11 for the left anterior descending coronary region; 21 and 22 for the right coronary region; and 17 and 24 for the left circumflex region. Other areas, commonly within the three regions, designated "probable", are shown by light shading in figure 2*b*. The remaining areas were considered "uncertain", as we could seldom tell to which of two regions they should be assigned. The common coronary distribution is depicted in figures 1 and 2. (b) Without too much loss of accuracy, each myocardial area could be symbolized by a square. It was then possible to design a linear arrangement of all the 24 areas so that the central and probable areas for each region are kept in groups, separated from each other by the uncertain areas, as in figure 2*c*. Insofar as possible, areas anatomically adjacent are kept so.† By appropriate symbols the character and amount of damage in each myocardial area could be designated. The charts thus show *distribution* accurately but indicate *amount* of damage only approximately, since they exaggerate the size of subendocardial and apical areas.

Results

We plotted the character and amount of damage appropriate to each area as compared with the coronary regions for each of our 44 cases of regional damage (including the two hearts with no damage). Hearts with damage in the same regions were kept together. All the (single) regional lesions were best subdivided into *large* and *small*: that is, those involving only a portion of one region and those involving

* The only variant of importance in this regard is a long left circumflex, supplying the branches to the posterior interventricular groove.[8] Nine patients had this coronary artery pattern (the usual pattern in animals) and will be identified in this report.

† A type of frequency diagram that preserves all major anatomical relationships actually was used in evaluating our data.

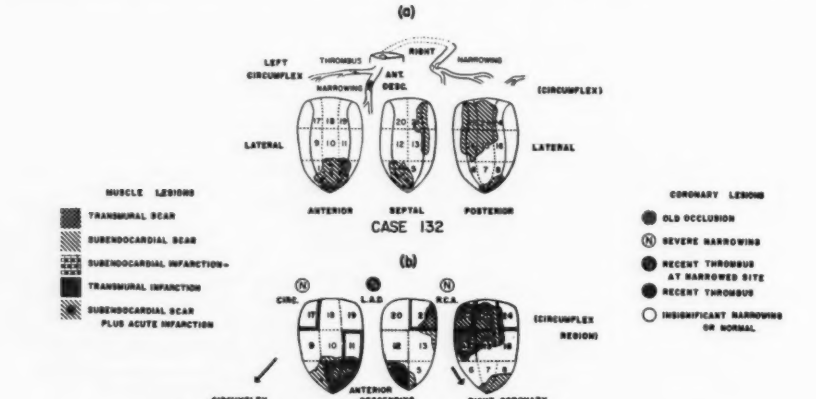

FIG. 2. Method of mapping and charting ventricular and coronary lesions. (*a*) Myocardial map of the left ventricle and septum based on their appearance after the hypothetical dissection illustrated in figure 1. While the levels of the actual ventricular slices can be shown in a myocardial map and were in fact used for the accurate transfer of necropsy data from slices to maps,[3] it is more convenient for the purpose of this paper, and corresponds well with conventional nomenclature, to consider the ventricle as divided into apical, basal and middle thirds. These form the lines of "latitude" for our map. The lines of "longitude" are provided by the interventricular grooves, the midlateral wall, and the middle of the septum. In addition it is useful to subdivide the anterolateral and the posterolateral segments into equal thirds by other lines of "longitude." Twenty-four subdivisions of the left ventricular and septal myocardium result. The relation of these muscle areas to the main coronary trunks is also indicated by the map. The heart illustrated has the common coronary arterial distributional pattern. The posteroseptal subendocardial scar and the anterior subendocardial scar can now be seen in their entirety. Acute necrosis in the vicinity of the anterior lesion, found on microscopic study, has been indicated by black dots.

(*b*) Simplified myocardial map of the same heart. Instead of isometric projection drawings, designed to show the edges and three-dimensionality of the myocardial segments, these are now symbolized by shield-shaped figures. The same lines of latitude and longitude are provided as in (*a*). The same lesions are shown but the thickness of lesions is now indicated only by the type of hatching (key at left). The coronary lesions are also shown by simplified symbols (key at right). The 24 myocardial areas have been given the same numbers seen in figures 1, *b c*, *d* and *e*, and 2*a*.

This figure illustrates how the numbered areas have been "assigned" to one or another region of supply for each of the major coronary arterial trunks. "Central" areas for each region are blocked out by heavy boundaries. Those myocardial areas probably within the distribution of any particular arterial trunks are lightly shaded. "Uncertain" areas, which might have been supplied in varying measure by either of two major coronary trunks, are left unshaded. The arrows and shaded zones show how the "central," "probable," and "uncertain" areas are related to the linear display below (*c*). Note that the greater simplicity of the two-dimensional shield-shaped drawings of the ventricular segments is at the expense of some distortion. The actual extent of the inner layers of the left ventricular and septal muscle is considerably less than the outer layers, as the isometric projection drawings indicate.

most of the region, including even some "probable" areas in adjacent regions. The results are shown in figures 3 and 4. The 56 hearts with widespread damage could be charted similarly. They also fell into two groups. In 36, the definitive lesions—the earliest that established the presence of widespread (bi- or triregional) damage—consisted of *healed scar* in the central areas of two regions. The remaining 20 patients were entitled to place in the "widespread" category only because of *acute damage* in the central areas of two regions, although some had had small amounts of old scarring in one region. We called these two subdivisions "widespread scar" and "widespread acute infarction". They are shown in figures 5 and 6.

1. *Survey of Four Basic Ventricular Myocardial Situations*

(a) Figure 3 shows all the hearts with small, single, regional lesions: group I. The predominantly subendocardial character of the damage (hatching) is apparent, as is the relatively limited extent of the lesions. A conspicuous feature of this group is the extent to which the anterior descending coronary artery region has been spared (see part 4). There was about an equal frequency of damage in the distributions of the right coronary artery and the circumflex. Occasionally it was not easy to decide whether a small lesion should be assigned to the right or the circumflex regions. We have rigorously based our final regional classification on the central areas aforementioned provided these were actually involved. (See legend, fig. 7.) One patient had strictly a right ventricular infarction, the only example of damage confined to this chamber. The two hearts without muscle damage are charted just below group I.

The coronary lesions of group I are also shown in figure 3, differentiation being made among narrowing, old occlusion and recent thrombosis, with or without a pre-existing narrowing. It will be noted that more than one-third of the group had only one coronary artery narrowed or occluded. However, the remainder, indistinguishable from the others so far as muscle lesions were concerned, had two or all three major arterial trunks partially or completely occluded. Recent thrombi were uncommon (20 per cent in this group and recent muscle damage the exception (36 per cent), half of the latter consisting of acute necrosis in the vicinity of ancient scars.

(b) Figure 4 depicts the muscle damage found in all the hearts having large regional lesions. These patients constitute group II. The tendency of massive lesions to spread into the border ("probable") areas of the other coronary regions is clearly shown. However, it can be seen that the central areas were not involved by massive damage (solid black or double cross-hatching) in more than one arterial region for each patient. There were, surprisingly, no true "lateral" infarctions of this massive, regional type although many of the large regional anterior lesions involved the apical third of the lateral wall and even its middle third. Myocardial rupture occurred in only one, case 3.

The coronary lesions of these patients were characterized by there being invariably a recent thrombus in the proximal portion of the regional artery for every acute infarct, usually associated with a previous severe narrowing of the vessel. However, only three patients failed to have severe narrowings or occlusions, old or recent, in two or even all three of their major coronary vessels. Right ventricular damage was common as an extension to the

(c) Linear rearrangement of the 24 myocardial areas. For simplicity all areas are represented by squares. This somewhat enlarges the eight apical areas, which contain less muscle than the other sixteen areas. Notations below the display relate the areas to conventional anatomic nomenclature. In each square the approximate extent of damage is shown, beginning with old scar, if any, at the bottom of the square and then any acute separate damage. Acute damage when present at the site of old scar is indicated by a large black dot, but without an attempt to express variations in extent Ages of scars are not symbolized.

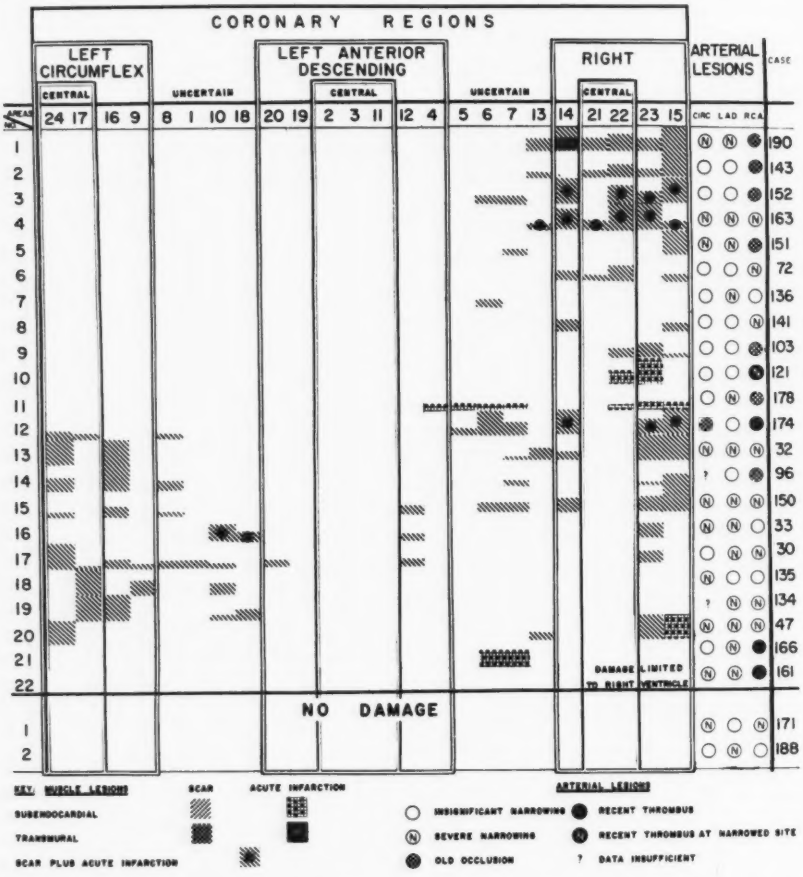

FIG. 3. The total myocardial damage picture of the 22 patients with small regional lesions and two in whom no damage was found at necropsy. Symbolism is the same as in figure 2*c*. The numbers on the left-hand side are for convenience of reference to particular cases. Actual case numbers are on the right of the arterial lesion symbols. A short right coronary artery (large circumflex) was present in case 22.

anterior wall from anterior lesions, and to the diaphragmatic surface from posteroseptal lesions. Mural thrombi in both the right and the left ventricle were also common. Important anatomic variants of coronary supply were common only in group II: a large left circumflex and short right coronary being found in five patients with anterior coronary regional damage.

(c) Figure 5 shows the "widespread scar" patients of group III. No differentiation is made here for the ages of scars. Three characteristics should be noted. (1) The typical lesion was subendocardial scarring (hatching), usually quite extensive, involving the central areas of two or all three coronary regions. Transmural scar was uncommon. (2) Acute damage was common but extremely variable in its character. Sometimes it consisted of transmural and sometimes of subendocardial damage: most often mixtures of acute damage and scar in the same area. (3) In the corresponding coronary artery an acute thrombus was often present, but the uniform finding was old ob-

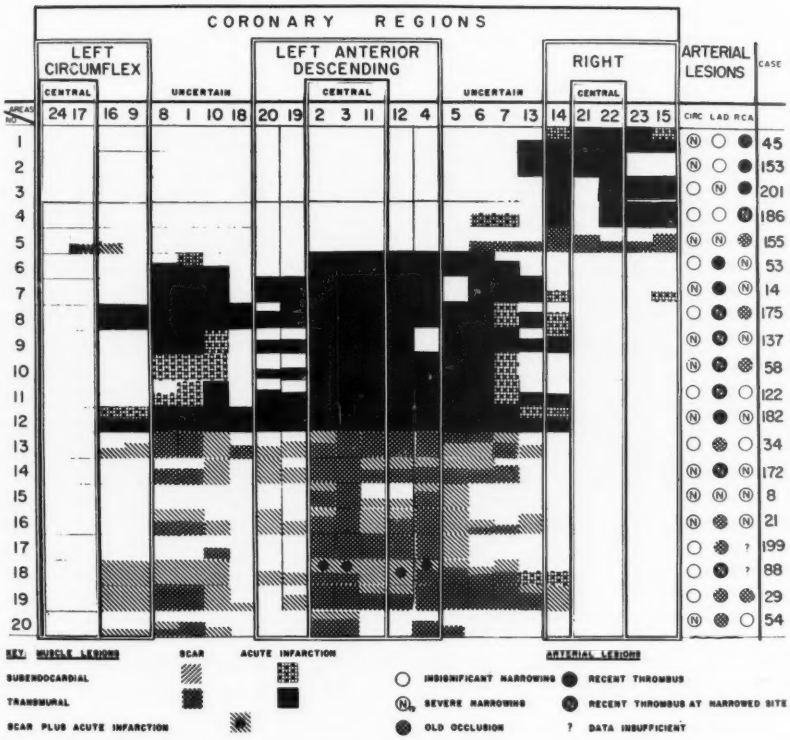

FIG. 4. The total myocardial damage picture for 20 patients with large regional lesions at necropsy. Symbolism is the same as in figure 2*c* and the legend to figure 3. A short right coronary artery (large circumflex) was found in cases 8, 9, 11, 14 and 19. In case 5, scar extended into a portion of one central area for the circumflex region, but the lesion was thought to be basically uniregional and is assigned to the right coronary region.

struction (severe narrowing or occlusion) of two or all three of the main coronary arteries.

(d) Figure 6 shows the "widespread acute infarction" patients of group IV. Three characteristics should be noted. (1) The common, prominent lesion was acute subendocardial infarction (checkered symbol). Acute damage was invariably widespread, involving the central areas of at least two regions in all but two instances. These had central area infarction in only one region, but damage involved the "probable" areas of all three coronaries in patterns indicative of bi-regional damage (cases 2 and 4). Damage tended to be more extensive and massive in hearts that had previously been scarred, these often being associated with an area of acute transmural damage (solid black) that might be slightly later in date. (2) When scar was present it was subendocardial, small in extent, and limited essentially to one region. (3) The characteristic coronary artery lesion was severe narrowing or old occlusion of two or all three of the major coronary trunks. It was common (60 per cent) to find recent thrombosis of a previously narrowed coronary artery, although this was not always the artery that appeared to have supplied the areas of most intense acute myocardial necrosis (cases 12, 13 and 18). In one instance, two recent thrombi were found. One patient's left *main* coronary artery was the seat of a recent thrombus. These, however, were very unusual situations that did not occur in the other groups.

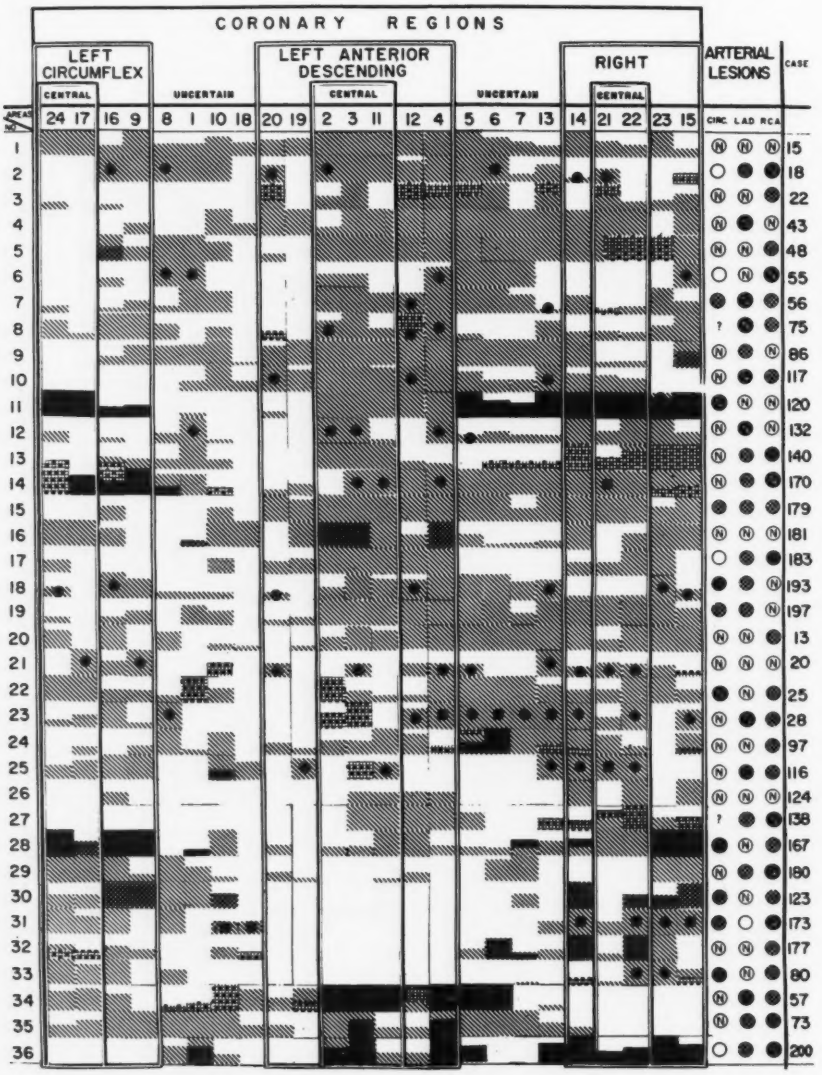

FIG. 5. The total myocardial damage picture for 36 patients with widespread scar (two or all three regions) at necropsy. Symbolism is the same as in figure 2*c* and the legend to figure 3. There was a large circumflex (small right coronary) in case 11.

(e) The four basic groups differed considerably both in behavior during life and in manner of death. Only a few of the patients with a small localized lesion (group I) were subject to the anginal syndrome. When death occurred in the presence of such minimal damage, it was due to "noncoronary" factors such as cerebral vascular lesions, or, in some hypertensive patients, to left ventricular failure.

In many patients with large localized lesions (group II) large acute infarctions befell the victims unheralded, or were preceded by only a short period of anginal distress. Once healed, these large lesions were seldom followed by

significant further damage. Sequelae of left ventricular failure, with or without embolism, were not infrequent. Some patients were almost asymptomatic, and died of unrelated conditions.

The order of events could often be discerned best from the historical and electrocardiographic data available for the majority of the widespread scar patients (group III). Two or more healed lesions, differing in histologic age, usually could be defined at necropsy, although a minority of the patients had widespread scar sheets not readily separable into areas of different histologic age. However, even in these latter hearts there was usually one separate older or more recent scar demonstrating the episodic character of at least some of the damage. Congestive heart failure was fairly common in this group, but "one more" terminal infarction was often the major cause of death.

The patients with widespread infarction (group IV) tended to have had frequent severe anginal pain attacks on relatively slight provocation, sometimes for years prior to the development of acute infarction. Sudden death was common. Often the clinical pictures suggested that infarction had been precipitated

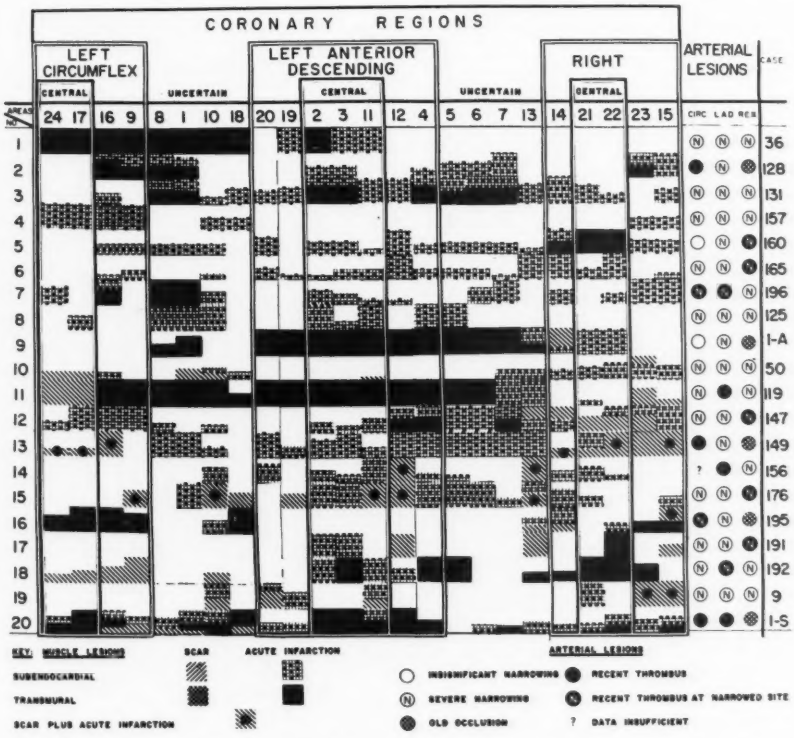

FIG. 6. The total myocardial damage picture of 20 patients with widespread acute infarction at necropsy. Symbolism is the same as in figure 2*c* and the legend to figure 3. *Two* recent thrombi occurred in case 7. In case 20 there was a recent thrombus in the previously-narrowed left *main* coronary artery at the site of a broken plaque, and one of the major divisions of the anterior descending coronary artery was occluded by atheroma (not indicated). The lateral scarring in case 13 was thought to be still in the right coronary region; otherwise the heart would have been classified with group III: A large circumflex (small right coronary artery) was found in cases 4 and 17. Both these hearts contained very early damage, the full extent of which was thought to be considerably greater than that recorded.

by acute anemia or blood pressure falls due to some unrelated disease.

2. *Analysis of Series by Lesions in Coronary Regions and Major Arteries*

Certain general characteristics of our sample of coronary disease can be quickly grasped if attention is first given only to the damage in central areas for each region. The upper bar graphs of figure 7 provide a summary of the type and frequency of central area damage by regions. It can be seen that subendocardial scarring was by far the commonest type of damage, occurring in 65 per cent of the patients (112 regions). Acute transmural infarction was next in frequency; in 28 per cent of the hearts (32 regions). A transmural portion of any lesion that was large enough to involve one "central" myocardial area led us to classify the whole lesion as "transmural" for the region in this bar graph summary. Acute subendocardial infarction and acute damage in the vicinity of old scar were equally common, each occurring in 16 per cent of the patients (24 and 25 regions respectively). Transmural scar was the least frequent type of damage, being found in 14 per cent of the patients (and 15 regions). It was common only among the large regional scars of the patients of group II.

From figure 7 it can also be seen that "old" coronary obstructions—occlusions or severe stenoses—were together overwhelmingly the

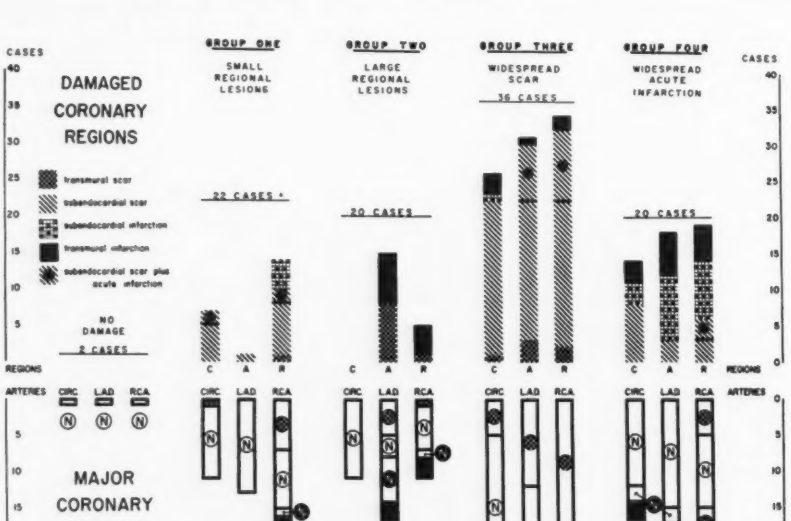

FIG. 7. Comparison of the muscle and coronary lesions in 100 patients having at least one severe coronary narrowing. The upper bar graphs denote myocardial damage in the *central* areas of each of the three major coronary regions. When the central area was spared, damage present in probable areas for the artery concerned was recorded except when it was considered to be an extension of a lesion lying mainly in an adjacent coronary region. Since the patients in groups I and II had damage limited to one region, by definition, the total height of the bar graphs for each of these groups equals the number of cases in the group. In the other groups there was always muscle damage in two or more regions at necropsy. Consequently the bar graph lengths total much more than the number of patients in the groups (compare fig. 8). Lesions in the coronary arteries supplying the major regions are summarized in the lower bar graphs.

commonest type of arterial lesions in the series. They involved each of the three coronary arteries with about equal frequency. Recent coronary thrombosis at a previously narrowed site was the next most common lesion. Recent thrombosis without severe pre-existing stenosis was less common still.*

Coronary obstructions were, indeed, far commoner than muscle lesions. This relationship is more easily seen when only the *old* muscle and coronary lesions are considered. Comparison of the hatched and cross-hatched portions of the upper bars and the "empty" portions of the lower bars in figure 7 gives a picture of the relative incidence of scar and obstruction presented by our series of patients before any of the acute infarcts or recent thrombi had appeared. It can then be seen that in group I, 61 per cent of the 66 major arterial trunks were obstructed. In group II, 55 per cent of the 60 major arterial trunks showed one or more old obstructions. In group III the incidence of old obstruction was 83 per cent for all three arteries, while in group IV it was 91 per cent.

Now, since our criteria for selecting the patients necessitated every heart having one arterial occlusion or severe narrowing, we must expect at least 33 per cent incidence of old obstruction and/or recent occlusion for the 126 major arteries in the regional damage groups (I and II). Furthermore it so happened that we never found scar without at least one severe narrowing in the regional artery. Thus in group III, with old damage in two or all three coronary regions, an incidence of old occlusion or severe narrowing might be expected in over 67 per cent of the 108 major arterial trunks. In group IV, with the great bulk of damage recent, the frequency of old coronary obstructions again need not have been higher than 33 per cent despite the presence of 12 small regional scars.

* It should be noted that one of the systematic errors of even a thorough autopsy is to exaggerate the number without narrowing because of failure to take a section through the narrowest portion of a thrombosed artery. (See part V.)[5]

3. *Combinations of Muscle Lesions. Interrelations Among the Basic Groups*

A comparison of the scar patterns (lesions at least a month old) with the total damage pictures at necropsy is given for the central areas of all patients in the bar graphs of figure 8. For groups III and IV the combinations of regions damaged are shown. Examination of our data in this form may throw light on interrelations among the basic groups and their natural history, as well as the structural basis for diagnosis in our sample prior to the development of myocardial situations that at necropsy were found to be in an acute or subacute stage.

A striking feature is that one out of four patients had an anatomically undamaged heart muscle prior to the terminal episode of infarction: 11 patients in group II, eight in group IV and four in group I, in addition to the two patients who had never had any muscle damage. Furthermore 30 additional patients, the remainder of groups I and IV, had damage in only one region or a part thereof. Yet the incidence of old coronary obstructions was much higher than expected for *both* the unscarred and the (small) regionally scarred hearts, as reference to the basic data in figures 3, 4 and 6 will show. Obviously, individual cases could not have been distinguished on the basis of the pattern of coronary narrowings and old occlusions alone.

Comparison of the upper with the lower bar graphs of figure 8 make it clear that the scar patterns alone would have been an inadequate basis for prognosis even if the presence and configuration of all scars were ascertainable. For example, the patients with no scar met at least three entirely different fates during the last month of life, as is shown in the lower bar graphs. There was, moreover, comparatively little difference in the lesions ultimately found at necropsy between certain patients with small regional scars and those with none, for both could develop terminal widespread acute infarction, as in group IV. On the other hand, small regional scars were common both in patients destined to suffer widespread terminal infarction and those in whom any acute

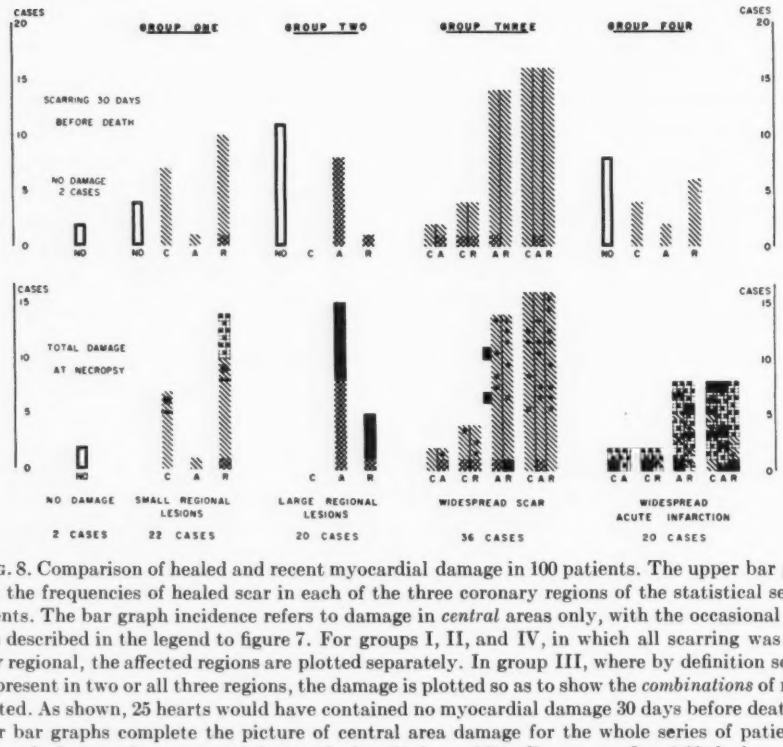

FIG. 8. Comparison of healed and recent myocardial damage in 100 patients. The upper bar graphs show the frequencies of healed scar in each of the three coronary regions of the statistical series of patients. The bar graph incidence refers to damage in *central* areas only, with the occasional exceptions described in the legend to figure 7. For groups I, II, and IV, in which all scarring was essentially regional, the affected regions are plotted separately. In group III, where by definition scarring was present in two or all three regions, the damage is plotted so as to show the *combinations* of regions affected. As shown, 25 hearts would have contained no myocardial damage 30 days before death. The lower bar graphs complete the picture of central area damage for the whole series of patients by adding the lesions that appeared during the last 30 days of life. For groups I and II the bar graphs, identical with those in figure 7 except for the change in scale, are for comparison. Groups III and IV have their total damage pictures plotted in terms of *combinations* of regions. Throughout, the total height of the bars or combinations of bars for each group is equal to the total number of patients in each group. Thus the whole of the present figure reflects case incidence of damage.

necrosis remained subregional and was considered only a contributory cause of death.

The descriptive names we have chosen for the groups, based as they are on muscle damage alone, can therefore be assigned to some of them at necropsy only. It can be seen from figures 7 and 8 that groups I and IV would have been indistinguishable on the basis of their muscle scars, although there was a statistically higher frequency of old coronary narrowing and old occlusions in group IV. The group III, "widespread scar," patients of course conformed to the same definition prior to the superimposition of recent damage. In group II the old scars were essentially unchanged, all of the large acute regional lesions developing in patients who had no previous muscle damage. Thus, at best, the scar patterns would have permitted classification of not more than 45 per cent of our patients had we been able to know the actual type and distribution of the damage. To have known whether the other 55 per cent had no damage or a single, small, regional scar would have been of little help so far as prognosis was concerned. It was characteristic of these patients that only their patterns of terminal acute damage revealed the extent and character of the low-threshold, localized ischemic areas that we believed represented the fundamental physiological difference between the groups. (See Discussion.)

While *undamaged* hearts became more common as we viewed the sample without charting any acute damage, certain myocardial situations remained surprisingly scarce. We still

found almost no small *healing* regional lesions (15 to 45 days old). Obviously all the small regional scars must have been in such a state at some time, but the chances of finding exactly this condition at necropsy would be small unless the patients were killed primarily by the infarctions in question. Furthermore the *combination* of one small regional scar with a *healing* small regional lesion was rare, presumably for the same reason. Most of the scarred hearts in group III must have had such a combination of lesions at *some* time, although we could not be sure that a few of the widespread scar sheets might not have been due to the healing of widespread subendocardial infarctions. Our data obviously do not justify the inference that lesions of this latter type must *always* be lethal.

Review of figures 7 and 8 enables us to make certain inferences concerning the order of development of coronary obstruction and ventricular muscle damage insofar as human coronary disease is exemplified by our series of patients. Coronary narrowing appeared to be the precursor of almost all the muscle damage we found, whether that damage resulted from gradually increasing stenosis, from circulatory stress, or was associated with coronary thrombosis at the narrowed point. Although only two hearts in this series had no muscle lesions *at necropsy*, there seems to be little doubt that narrowing without regional muscle damage is a common situation *during life* but seldom found at necropsy because it is rarely lethal. Certainly it must have existed in one-fourth of our patients a few weeks before they died. Old coronary obstruction (narrowing or occlusion) without muscle damage also must have been the precursor state for all the patients with small regional scars in groups I and IV.

The combination of one small, regional subendocardial scar and one healing, regional infarction elsewhere in the heart would provide a picture transitional between the small regional lesions of group I and the multiple or widespread lesions in group III. It could scarcely be doubted that many of our widespread scar patients at one stage must have been developing their muscle damage picture in such a manner. We have, however, rarely seen hearts with one small regional scar plus a separately placed acute, *small* infarction confined to a second region at necropsy, and no instances occurred in the basic series.

It has already been mentioned that the "widespread infarction" hearts of group IV that had scarring would have been almost indistinguishable anatomically, prior to the development of their terminal lesions, from the small regional scars of group I, although the degree of coronary stenosis tended to be more severe in group IV. Thus, a group I anatomic picture upon occasion may be a precursor state for group IV. Although it is possible that a group I state might be a precursor for occasional patients of group II type (with a healed lesion formed by repeated infarctions all within one coronary artery's distribution), we have elicited no definite evidence that such a relationship had existed in any of our cases. Obviously certain transitions between the groups would be impossible. Scars do not disappear and their presence limits the possible transitions for those hearts.

4. *Peculiarities of the Frequency and Anatomic Location of the Common Types of Muscle Damage*

Because there was little difference in the overall incidence of coronary lesions among the three major regional arteries, it might be expected that damage in each of the three regions would not differ greatly in type or frequency. This was not so. (a) Small, *isolated* anterior regional lesions were rare, whereas small isolated right or circumflex regional lesions were common. (b) No large *isolated* circumflex regional ("lateral") infarcts or scars were found at all. (c) Among the widespread damage hearts, the combinations of damaged regions that included the central areas of *both* the anterior and the right ("posterior") coronary regions were much commoner than the other combinations.

(a) When anterior regional lesions occurred alone, they were common only as the massive infarcts and scars of group II. There were, indeed, three times as many of the latter as posteroseptal lesions of the same type. In contrast, almost every other lesion affecting

TABLE 1.—*Salient Anatomic Characteristics and Certain Clinical Features of the 4 Basic Myocardial Damage Groups*

	Group I (22 cases) Small, Regional Lesions	Group II (20 cases) Large, Regional Lesions	Group III (36 cases) Widespread Scar	Group IV (20 cases) Widespread Infarction
Characteristic muscle lesions	Single subendocardial scar, acute damage sometimes intermingled. Rarely one regional subendocardial acute infarction	Transmural damage: scar or acute infarction, usually not both	Subendocardial scarring: multiple lesions or a widespread. sheet. Commonly a terminal acute lesion also	Acute subendocardial infarction. Transmural portion occasionally. Scar small and regional or absent. Two recent lesions rare
Damage distribution	Anterior coronary region spared. Damage posterior or lateral mainly	Heaviest at apex or posteroseptal region of left ventricle. Right ventricular extensions common	Scar almost anywhere in left ventricle or septum. Earliest lesion usually posterior or lateral. Acute damage at scar sites or separate	Variable distribution. Sometimes too recent to be mapped in detail. Scar posterior or lateral, if any
Recent coronary thrombus	Uncommon (19%)	In artery supplying any acutely infarcted area	One in 61%	One in 65%. Sometimes not in "expected" artery. Rarely two
Old coronary obstruction (narrowing or occlusions)	One or more arteries. Single artery in 50%	One or more arteries. Single artery in 35%	Two or more arteries	Two or more arteries
Clinical features	Angina sometimes. Death not directly due to muscle damage or ischemia	Short history or none. Death from effects of acute infarction, embolism or left ventricular failure	Long histories. Multiple episodes of clinical "acute infarction". Failure common	Severe anginas; sudden deaths. Precipitation of infarction by acute exertion, anemia, or hypotension
Background picture: 30 days premortem	Little changed. One small scar, rarely no damage	No lesion or a single large, regional scar	Relatively little change, but slightly less damage	No lesions or one small, localized scar
Precursor state	Coronary obstruction without muscle damage	Coronary obstruction without muscle damage	Small, regional lesion, as in Group I	Group I (if scar); coronary obstruction without damage

the anterior region was part of a widespread or "multiple-region damage" situation. Since small regional lesions were fairly common it followed that these were in the right or left circumflex coronary distribution almost invariably; that is, "posterior", "posteroseptal", "posterolateral" or "lateral" in their location. This was true not only of the small regional lesions of group I: almost all the old lesions found in the majority of the "widespread acute infarction" hearts of group IV were also small and regional. Furthermore, less than one fifth of the hearts with widespread healed damage (group III) presented clear-cut evidences that the anterior coronary region had been involved before the others, while the majority could be shown to have had preexisting damage in the right coronary or the left circumflex regions, or both, as their initial ventricular muscle lesion. The widespread acute infarcts of group IV, however, appeared to affect any two of the three regions with comparable frequency. *Thus, with the exception of the large regional lesions (group II), and the minority of group IV in which the first damage to the heart was widespread infarction, muscle damage in the left ventricle tended to begin in regions other than the anterior.*

(b) The low frequency of large circumflex regional ("lateral") lesions has already been mentioned in the description of group II. Lateral damage was seen only as small, regional scars or as part of a widespread damage situation. In the latter circumstance almost any type of lateral wall involvement could be expected. These peculiar relationships are summarized in figure 7.

(c) The widespread damage *combinations* graphed in figure 8 also show a much higher incidence of anterior-plus-right-coronary-region damage and of damage in all three regions, as compared with either anterior-plus-circumflex or right-coronary-plus-circumflex-region damage. Thus, we can say that circumflex region ("lateral") damage, common in hearts with widespread lesions, was much more often found in association with *both* right and anterior coronary region damage than with either one alone. To state the same fact in another way: the *combinations* of damaged regions that included the "whole" septum were remarkably common in both widespread damage groups. It was uncommon to find combinations in which *either* the septum's posterobasal area (case 21, supplied by the right coronary) *or* its anterior apical areas (cases 4, 5 and 12, supplied by left anterior descending) were anatomically intact.

We have observed no correlation between these peculiarities of lesion location and combination, and the location of disease in the individual coronary vessels. The frequencies of old lesions in the major regional arteries were much the same, as figure 7 shows. The over-all frequency of severe narrowing or old occlusion was 82 per cent for the left anterior descending, 79 per cent for the right coronary artery, and 89 per cent for the left circumflex. Recent thrombi had only one third the frequency of old lesions. They were less frequent in the left circumflex than in the other two major regional arteries.

The salient features of the myocardial situations described so far are summarized in table 1.

(To be concluded in the October issue)

An Evaluation of the Effect of Continuous Long-Term Anticoagulant Therapy on the Prognosis of Myocardial Infarction:

A Report of 82 Cases

By M. M. SUZMAN, M.D., M.R.C.P., H. D. RUSKIN, M.B., M.R.C.P., AND B. GOLDBERG, M.D., M.R.C.P.

Eighty-two patients who survived a myocardial infarct were treated continuously with anticoagulants for periods of 3 to 76 months. Another 88 patients whose treatment with anticoagulants was limited to the acute phase of an infarction and who were observed for similar periods acted as a control group. The group treated continuously exhibits a lower mortality rate with fewer recurrences of infarction. Among the factors subjected to statistical analysis and found to influence the ultimate prognosis unfavourably and which therefore serve as indications for long-term anticoagulant therapy, are a severe presenting attack and a history of previous infarction.

A LONG-TERM clinical study was undertaken to determine whether the prognosis of myocardial infarction could be improved by anticoagulant therapy continued indefinitely after recovery from the acute phase of the disease. Since the beneficial effect of anticoagulants in acute arterial thrombosis was thought to be largely prophylactic in the sense that further thrombus formation or the propagation of an existing thrombus may possibly be prevented, it was considered rational to apply this therapy on a long term basis with a view to preventing recurrences of coronary thrombosis and myocardial infarction.

Furthermore, since atheroma is generally accepted as the underlying pathological process responsible for the ultimate precipitation of acute occlusion by thrombosis as well as for progressive coronary artery narrowing, it was considered of fundamental importance that an experimentally produced intra-arterial thrombus, after having undergone organization and endothelialization, presents eventually as a lesion histologically indistinguishable from that of atheroma even to the extent of exhibiting the characteristic fatty changes, calcification and ulceration.[1-4] Based on the concept that atheroma may result from intra-arterial mural thrombus formation rather than, as is currently thought, from a lesion of obscure metabolic origin arising subendothelially in the vessel wall, the long continued administration of anticoagulants would appear to be rational therapy for the prevention of progressive coronary artery disease.

The first long-term anticoagulant regime for myocardial infarction to be instituted in this series was commenced in November 1946 in a 60 year old man with a history of three previous attacks. The treatment was carried out continuously until his death from a recurrent infarction in September 1949. When it was realized that the continuous long-term use of anticoagulants was a practical and relatively safe procedure with prothrombin levels estimated at intervals of one or two weeks, this regimen was gradually adopted for the treatment of more patients with myocardial infarction.

As the aim of this clinical study was to assess specifically the possible value of anticoagulant therapy given continuously on a long-term basis, it was considered advisable that a control series of patients with myocardial infarction should be observed parallel with the treated

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series and moreover that this control group should be comprised only of patients who had received anticoagulant therapy for a period of time limited to the acute phase of the disease. In this way a comparison could be made between the effects of short-term and long-term anticoagulant therapy rather than between anticoagulant therapy and no such treatment. Furthermore, any difference noted in the prognosis of the patients receiving long-term anticoagulant therapy could not then be interpreted as a remote effect of the anticoagulants given during the acute phase of the disease. Consequently, patients with myocardial infarction who did not receive anticoagulant therapy during the acute phase were excluded from the control group.

Materials and Methods

Two hundred and eight patients, having received anticoagulant therapy during the acute phase of an attack of myocardial infarction, who survived for three months or more, were followed until their death or until the end of the period of the authors' study (Sept. 1, 1953).

Of the 208 patients, 120 received anticoagulants continuously for three months or longer, but 38 of these discontinued the treatment after periods ranging from 3 to 30 months or were treated intermittently and are therefore excluded from this comparative study. Thus, 82 patients have received anticoagulant therapy continuously for periods ranging from 3 to 76 months, and are designated the "long-term group". Eighty-eight patients who received anticoagulant therapy only for a period of time limited to the acute phase of the presenting attack or of subsequent attacks of myocardial infarction and who were observed for periods ranging from 3 to 72 months serve as controls and are designated the "short-term group".

Selections of Patients for Long-Term Therapy

The patients were drawn from unselected hospital admissions and private practice and the two groups run parallel in time over a period of up to 76 months. After the patients had recovered from the acute phase of the disease, the question of whether or not to continue with anticoagulant therapy for an indefinite period was raised with the patient and the family doctor. The reasons for advocating this form of treatment were fully explained in simple language and the implications of embarking on such a regime were pointed out. The need for regular attendance at the clinic and the laboratory and the inherent dangers of anticoagulant therapy were stressed. Persuasion was not resorted to and the final decision was left to the patient.

In the patients who had suffered previous episodes of myocardial infarction and in those whose presenting attacks were severe, there was a tendency to accept this regimen more readily than in the patients experiencing their first attack, particularly if it happened not to be severe. In those for whom adequate laboratory facilities were not available, such as patients living in the country districts, it was explained that the regimen could not be contemplated unless the patient was prepared to make regular visits to a laboratory. Those who declined or were unable to undertake the continuous treatment constituted the group which serves as a control.

A number of patients commenced the treatment but discontinued after varying periods for different reasons. Reports in the lay press and unsolicited advice from friends, stressing the danger of hemorrhage with the use of Dicumarol, influenced a further group. Some patients found the need for regular attendance at the laboratory tiresome or inconvenient and in others the deciding factor was the onset of hemorrhagic complications, which even when mild sometimes served as an excuse for terminating the anticoagulant regimen.

Anticoagulant Medication

During the acute phase of myocardial infarction heparin was used initially in the majority of patients for periods ranging from one day to three weeks, the average duration being five to seven days, in the dosage which maintained the blood clotting time at approximately twice the normal. A day or two before discontinuing the heparin, an orally effective anticoagulant was commenced and discontinued after periods ranging from three weeks to three months in the patients of the short-term group, but continued indefinitely in those comprising the long-term group.

Dicumarol was the oral anticoagulant most commonly used. Tromexan was given a trial in several cases but control was found to be difficult. Recently phenylindandione has been used extensively and Cumopyran in a few patients. The required dosage of Dicumarol and phenylindandione has been found to vary widely in the same and different patients. The weekly maintenance dose of Dicumarol ranged between 150 and 1,100 mg., and of phenylindandione between 125 and 700 mg. with an average in the majority of patients for both drugs of 350 to 450 mg.

Control of Long-Term Anticoagulant Therapy

Prothrombin control was maintained in all patients. After a satisfactory level had been obtained, the test was carried out at weekly or two-weekly intervals, while in some of the patients, in whom

the prothrombin level remained constant over many months, the intervals were increased to three or even four weeks. When wide fluctuations occurred, more frequent determinations were carried out until a steady level had again been restored. The optimum therapeutic level aimed at was a prothrombin time of twice the normal and was expressed as a percentage, the prothrombin index (P.I.).

The prothrombin level was estimated by the Quick one-stage method or modifications thereof, in the majority of cases, but recently a simplified bed-side method using capillary blood, as described by Stein and Wallace,[5] has been adopted for patients attending the clinic and found to be satisfactory. A series of parallel determinations using this simplified capillary method and the standard technique were found to show a good correlation.

The optimum therapeutic range was arbitrarily fixed at a prothrombin index of 40 to 60 per cent. In 70 per cent of the cases the prothrombin level was maintained in the therapeutic range more or less constantly. In 20 per cent wider fluctuations occurred and it was necessary to vary the dosage of anticoagulant from time to time in an attempt to maintain a more constant level. In approximately 10 per cent of the cases the control was considered to be poor, in that wide inexplicable fluctuations occurred frequently and difficulty was experienced in maintaining the prothrombin levels within the therapeutic range.

Observations and Results

Toxic Effects of Long Term Anticoagulant Therapy

Hemorrhage of varying degrees of severity occurred in 12 cases. Nine patients had hematuria and there was one instance each of epistaxis, of melena and of hemarthrosis involving a shoulder joint. Several of these patients also exhibited easy bruising of the skin.

In the majority, merely stopping the administration of the anticoagulant temporarily or reducing the dose sufficed to control the hemorrhage, but where bleeding persisted the use of a vitamin K derivative, more particularly synthetic vitamin K_1 (Konakion) given orally in a single dose of 10 to 20 mg. proved effective. Two patients died of hemorrhage while receiving Dicumarol. In one case, a hypertensive male aged 49 years, death resulted from a cerebral hemorrhage four months after the presenting attack of myocardial infarction. As the prothrombin index was 50 per cent at the time of the cerebrovascular accident and there were no other hemorrhagic manifestations, Dicumarol was not considered to be a contributory cause. In the other case, a 62 year old male, in severe congestive cardiac failure which had persisted since the presenting attack of myocardial infarction four months previously, and in whom the prothrombin control had been poor, a massive gastrointestinal hemorrhage occurred without other signs of bleeding. Although with the use of vitamin K and blood transfusions the bleeding ceased and the anemia was corrected, the patient died in congestive cardiac failure. Dicumarol was considered an indirect contributory cause in hastening the death of this patient.

Of the 38 patients who discontinued long term therapy, 15 did so because of the onset of hemorrhagic manifestations, but in none of these was the bleeding considered severe enough to have warranted permanent discontinuation of the anticoagulant regime.

Table 1.—*Age Distribution*

Age in Years	Numbers of Cases	
	Long Term	Short Term
30–39	4 (4.9%)	6 (6.8%)
40–49	31 (37.8%)	25 (28.4%)
50–59	26 (31.7%)	33 (37.5%)
60–69	17 (20.7%)	19 (21.6%)
70 and over	4 (4.9%)	5 (5.7%)
Totals.....	82	88

Composition of Long and Short Term Groups

Age: Table 1 shows that there is a slight difference in the age distribution in the two groups. Fifty-seven per cent of the long-term group and 65 per cent of the short-term group were patients over the age of 50 years. The differences are not statistically significant ($x^2 = 1.90$; $0.80 > p > 0.70$)* and there is no indication that age played a part in the selection of the patients for inclusion in one or other groups or that it could have influenced the ultimate prognosis.

* The statistical analyses were kindly carried out by Dr. Julian Hoffman, Medical Registrar, Johannesburg General Hospital.

TABLE 2.—*Sex Distribution*

	Numbers of Cases	
	Long Term	Short Term
Male	72 (87.8%)	71 (80.7%)
Female	10 (12.2%)	17 (19.3%)
Totals	82	88

Sex: There were slightly more females in the short-term group, as seen in table 2, but statistically the difference is insufficient to have influenced either the selection of the group or the final results. ($x^2 = 1.12$; $0.30 > p > 0.20$).

The Incidence of Previous Coronary Artery Disease in Long and Short Term Groups

The number of patients in each group with a previous history of angina, of angina with infarction and of infarction only, as well as those without a previous history of coronary artery disease are tabulated in table 3 and figure 1.

It will be seen that in the long-term group, 19 patients had previous angina alone and 39 had no previous coronary artery disease, whereas in the short-term group 12 patients had previous angina alone and 59 had no previous coronary artery disease. The difference between the two groups in respect of the incidence of previous angina alone, that is, without infarction, shows an excess in favor of the long-term group, but the difference is not statistically significant. ($x^2_E = 3.55$; $0.10 > p > 0.05$).

TABLE 3.—*Incidence of Previous Coronary Artery Disease*

Previous Coronary Artery Disease	Numbers of Cases	
	Long Term 82	Short Term 88
Angina only	19 (23.2%)	12 (13.6%)
Angina and infarction	14 (17.0%)	12 (13.6%)
Infarction only	10 (12.2%)	5 (5.7%)
None	39 (47.6%)	59 (67.0%)
Total with angina	33 (40.2%)	24 (27.3%)
Total with infarction	24 (29.3%)	17 (19.3%)

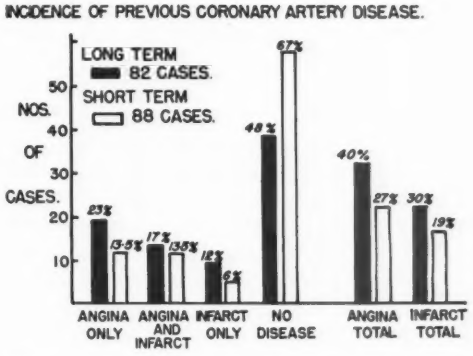

FIG. 1. Incidence of Previous Coronary Artery Disease

Previous myocardial infarction was found to have occurred in 24 patients in the long-term group and in 17 in the short-term group. The difference, whether estimated in relation to the total number of patients in each group ($x^2_E = 1.78$; $0.30 > p > 0.20$) or to the number of patients without previous coronary artery disease ($x^2_E = 3.39$; $0.10 > p > 0.05$), is found not to be statistically significant. However, when the total incidence of previous coronary artery disease in the two groups is compared, namely 43 patients in the long term-group (52.4 per cent) and 29 in the short-term group (33.0 per cent), the difference is found to be statistically significant ($x^2_E = 5.93$; $0.02 > p > 0.01$).

This difference would appear to indicate that a previous history of coronary artery disease could have influenced the decision whether or not to embark on a continuous long-term anticoagulant regime and also must be taken into account in the assessment of the subsequent prognosis.

Degree of Severity of Presenting Attack of Myocardial Infarction

The patients in both groups are separated into those whose presenting attack was considered to have been uncomplicated, designated "mild" in this communication, on the one hand or complicated, designated "severe", on the other. The assessment of the degree of severity is based on accepted clinical criteria as observed during the course of the acute

phase of the disease or in retrospect after recovery, rather than, at the time of the onset of the attack as is advocated by some workers in this field.[6, 7] The mild cases exhibited no shock and little or no fall in blood pressure. Pain, which if severe, was only of short duration and readily controlled by medication. Arrhythmias, other than occasional extrasystoles, were absent; there was no gallop rhythm, cardiac failure, cardiac enlargement or thromboembolic complication. These patients were not clinically ill and often felt none the worse for their coronary episode. Their recovery was rapid and residual symptoms such as tachycardia, breathlessness and weakness were absent. At first an attempt was made to subdivide all patients who were not considered to have had a mild attack into "moderate" and "marked," but difficulties were encountered in making a sharp distinction between these categories, so that all of these patients have been combined in one group designated "severe."

The diagnosis was confirmed in all cases by electrocardiography and in the majority of instances 12-lead tracings were obtained. The clinical assessment of the degree of severity could frequently be confirmed by the extent of the electrocardiographic changes.

Table 4 shows the numbers of patients in the long- and short-term groups whose presenting attacks were mild or severe. It will be seen that in the long-term group there were fewer mild and more severe attacks, that is 18.3 per cent and 81.7 per cent, respectively, than in the short-term group in which 31.8 per cent were mild and 68.2 per cent severe. Analysis of these figures would appear to indicate that there was a strong tendency, though not statistically significant ($x_E^2 = 3.35$; $0.10 > p > 0.05$), for the degree of severity of the presenting attack to have been a factor in deciding whether or not the anticoagulant therapy should be continued indefinitely.

TABLE 4.—*Degree of Severity of Presenting Attack of Myocardial Infarction*

	Numbers of Cases	
	Long Term	Short Term
Mild	15 (18.3%)	28 (31.8%)
Severe	67 (81.7%)	60 (68.2%)
Totals	82	88

Duration of Observation and Mortality in the Long- and Short-Term Groups

The duration of observation of the patients receiving long-term continuous anticoagulant therapy and of the short-term controls has varied between 3 and 76 months, and is set out in table 5 and depicted in figure 2. As will be seen in the long-term group, a somewhat greater number of patients were observed for less than one year and fewer for four years or more. These differences are found not to be statistically significant ($x_E^2 = 2.55$; $0.20 > p > 0.10$).

Table 5 and figure 2 also show the mortality at varying periods of observation. It will be seen that all the deaths in the long-term group and the majority in the short-term group occurred before the end of the fourth year of observation. The total number of deaths in the long-term group was six (7.3 per cent) and in the short-term group 29 (33 per cent). This marked difference in mortality between the two groups is statistically highly significant ($x_E^2 = 15.54$; $p = 0.001$).

When a comparison is made (table 6 and fig. 3) of the severe cases of myocardial infarction in the long- and short-term groups by

TABLE 5.—*Duration of Observation and Mortality. The Numbers of Patients, Alive or Dead, Observed for Varying Periods*

Duration Months	Long Term			Short Term		
	Total	Alive	Dead	Total	Alive	Dead
3–11	19	16	3	13	4	9
12–23	17	16	1	18	10	8
24–35	19	18	1	19	12	7
36–47	17	16	1	18	15	3
48–59	6	6	—	12	10	2
60–71	3	3	—	7	7	—
72+	1	1	—	1	1	—
Totals	82	76	6	88	59	29
Percentage		92.7	7.3		67.0	33.0

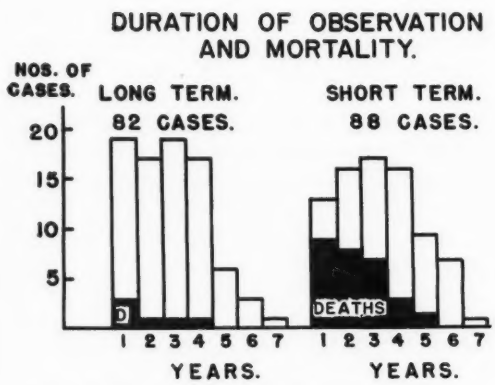

FIG. 2. Duration of Observation and Mortality

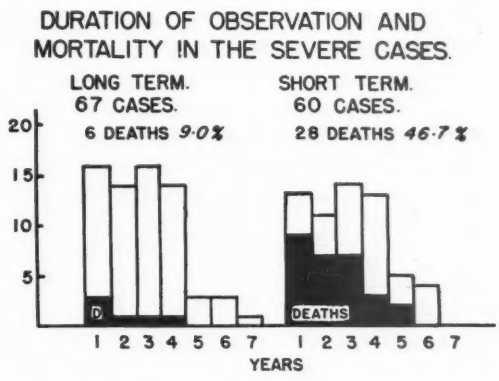

FIG. 3. Duration of Observation and Mortality in the Severe Cases

eliminating those in which the presenting attack of infarction has been mild, it is found that the distribution of the patients in the two groups in terms of duration of observation becomes more similar and the excess of patients living more than four years in the short-term group becomes less apparent ($x_E^2 = 0.24$; $0.90 > p > 0.80$). This is due to the fact that of the 18 patients in the short-term group who lived four years or longer, 11 were mild cases, whereas of the 10 patients living four years or more in the long-term group only three had suffered mild attacks of myocardial infarction. With the elimination of the mild cases the mortality is found to be 9 per cent in the long-term group and 46.7 per cent in the short-term group, a difference which is highly significant ($x_E^2 = 20.99$; $p < 0.001$). Of the total number of 43 patients considered to have had a mild attack only one died and this occurred in the group not receiving continuous anticoagulant therapy. The difference in the mortality of the patients with mild and severe attacks of infarction is striking. The comparative incidence of subsequent complications will be dealt with later.

TABLE 6.—*The Duration of Observation and Mortality in the Severe Cases of Myocardial Infarction*

Duration Months	Long Term			Short Term		
	Total	Alive	Dead	Total	Alive	Dead
3–11	16	13	3	13	4	9
12–23	14	13	1	11	4	7
24–35	16	15	1	14	7	7
36–47	14	13	1	13	10	3
48–59	3	3	—	5	3	2
60–71	3	3	—	4	4	—
72+	1	1	—	—	—	—
Totals....	67	61	6	60	32	28
Percentage.....		91.0	9.0		53.3	46.7

Age and Sex in the Fatal Cases (table 7)

Since age and sex are considered to be factors influencing the prognosis of myocardial infarction their effect on the mortality was statistically estimated. No significant differences were noted in the mortality in relation to age ($x_E^2 = 0.13$; $0.95 > p > 0.90$). In the series as a whole or in a comparison between the long- and short-term groups, sex was not a factor influencing the subsequent mortality ($x_E^2 = 1.14$; $0.30 > p > 0.20$).

TABLE 7.—*Age and Sex in the Fatal Cases*

Age in Years	Long Term—82 Cases			Short Term—88 Cases		
	Total	Male	Female	Total	Male	Female
30–39	0	—	—	3	3	—
40–49	2	2	—	4	4	—
50–59	1	1	—	12	9	3
60–69	3	2	1	8	6	2
70+	0	—	—	2	2	—
Totals....	6	4	1	29	24	5

The Incidence and Mortality of Subsequent Complications

Table 8 shows the incidence and mortality of the complications which occurred during the periods of observation in both groups.

Myocardial Infarction. Subsequent myocardial infarction occurred in seven (8.5 per cent) of the 82 patients in the long-term group and in 24 (27.3 per cent) of the 88 patients in the short-term group. The difference in the incidence of subsequent infarction in the two groups is marked and is found to be statistically significant ($x^2_E = 8.77$; $p < 0.01$). In the long-term group, three of the seven patients with recurrent infarction died (mortality 42.8 per cent) and in the short-term group 19 of the 24 (mortality 79.1 per cent). The difference shows a tendency for decreased mortality from recurrent myocardial infarction in the patients treated with anticoagulants continuously as compared with those not so treated, but the figures are too small for accurate computation and therefore cannot be considered statistically significant ($x^2_E = 2.93$; $0.10 > p > 0.05$).

Cardiac Failure. Subsequent cardiac failure occurred in 19 (20.7 per cent) patients in the long-term group and 14 (15.9 per cent) patients in the short-term group indicating a slightly greater tendency for this complication to occur in the anticoagulant treated patients, but the difference in the incidence is not significant ($x^2_E = 1.01$; $0.50 > p > 0.30$). However, a marked difference is noted in the mortality due to cardiac failure. Of the long-term cases, only two (11.8 per cent) died, whereas there were eight deaths (57.1 per cent) due to cardiac failure in the short-term group. These differences are significant ($x^2_E = 6.11$; $0.02 > p > 0.01$).

A fatal cerebral hemorrhage caused the death of one patient in the long-term group, a 49 year old male, four months after the attack of infarction, and of one patient in the short-term group, a 76 year old male, 20 months later. Both were hypertensive, and in the case of the patient receiving anticoagulants, it is most unlikely that the hemorrhage was due to Dicumarol toxicity, as the prothrombin index at the time of the episode was 50 per cent and, furthermore, no hemorrhagic manifestations were evident elsewhere. One patient, a 36 year old male, in the short-term group, died as the result of cerebral embolism, 20 months after the presenting attack of myocardial infarction.

In the long-term group, subsequent complications other than angina occurred in a total of 27 patients (32.9 per cent) of whom six (22.2 per cent) died, whereas in the short-term group 40 (45.4 per cent) patients had suffered subsequent complications other than angina of whom 29 (72.5 per cent) died. Although there is a greater tendency for these complications to have occurred in the patients of the short-term group, the difference is not significant ($x^2_E = 2.83$; $0.10 > p > 0.05$). The overall difference in the mortality resulting from these complications, however, is very markedly in favor of the patients receiving long term anticoagulant therapy ($x^2_E = 13.54$; $p < 0.01$).

The Incidence of Angina Pectoris Subsequent to the Presenting Attack of Myocardial Infarction. Following the presenting attack of myocardial infarction, the incidence of angina was approximately the same in the two groups, 41 of the 82 long-term and 39 of the 88 short-term

TABLE 8—*Incidence and Mortality of Subsequent Complications*

Subsequent Complications	Long Term 82 Cases		Short Term 88 Cases	
	Incidence	Mortality	Incidence	Mortality
Myocardial Infarction	7 (8.5%)	3 (42.8%)	24 (27.3%)	19 (79.1%)
Cardiac Failure	19 (20.7%)	2 (11.8%)	14 (15.9%)	8 (57.1%)
Cerebral Hemorrhage	1	1	1	1
Cerebral Embolism	—	—	1	1
Totals	27 (32.9%)	5 (22.2%)	40 (45.4%)	29 (72.5%)

TABLE 9.—*Angina Pectoris Subsequent to Presenting Attack of Myocardial Infarction*

	Long Term—82 Cases	Short Term—88 Cases
Angina	41	39
Improved	23 (56%)	9 (23%)
Died	3 (7.3%)	14 (35.8%)

patients having suffered from this condition (table 9). The subsequent course in respect of the angina, however, differed to a marked extent in the two groups. Relief or marked improvement occurred in 23 (56 per cent) of the long-term group but in only nine (23 per cent) of those not receiving anticoagulants. This difference is statistically significant ($x_E^2 = 7.75$; $p < 0.01$).

The Relation of the Severity of the Presenting Attack of Myocardial Infarction to the Incidence of Subsequent Cardiac Complications and Deaths

Since it is known that the degree of severity of an attack of myocardial infarction profoundly influences the ultimate prognosis, a comparison is made (table 10) between the mild and severe cases in respect of the incidence of subsequent complications and deaths of cardiac origin. Of the total number of 170 patients in this series, the attack was mild in 43 (25 per cent) and severe in 127 (75 per cent). Of the 15 patients in the long-term group who had experienced mild attacks, five (33 per cent) suffered from subsequent angina, but there were no instances of subsequent myocardial infarction or cardiac failure and there were no deaths. Of the 28 patients with mild attacks in the short-term group, angina occurred in nine (32 per cent), indicating no difference in the incidence of this sequel, but myocardial infarction occurred in three patients (11 per cent) of whom one (4 per cent) died.

The incidence of subsequent complications and deaths is so small in patients whose presenting attack of myocardial infarction had been mild, that statistical computation of the differences between the two groups is not possible. It is of interest that when myocardial infarction and deaths did occur, they are to be found in the group of patients not receiving continuous anticoagulant therapy.

The very low incidence of subsequent complications and fatalities in the mild cases is in sharp contrast to that found in patients whose presenting attack of myocardial infarction had been severe. In a comparison of the mild and severe groups (table 10), each as a whole, angina occurred somewhat less frequently

TABLE 10.—*Relation of Severity of Presenting Attack of Myocardial Infarction to Incidence of Subsequent Cardiac Complications and Deaths*

	Mild—43 Cases (25%)		Severe—127 Cases (75%)	
	Long Term	Short Term	Long Term	Short Term
Nos. of Cases	15	28	67	60
Angina...	5 (33%)	9 (32%)	36 (54%)	30 (50%)
Infarction	—	3 (11%)	7 (10%)	21 (35%)
Failure...	—	—	19 (28%)	14 (23%)
Deaths...	—	1 (4%)	5 (7%)	26 (43%)

amongst the mild (32.5 per cent) than the severe cases (51.9 per cent), but the difference in the incidence of recurrent myocardial infarction, of cardiac failure and of fatalities was very marked and highly significant. It is obvious that in evaluating the prognosis of acute myocardial infarction, separate consideration must be given to mild and severe cases.

A comparison of the long and short-term groups in respect of severe cases shows a difference, which is statistically highly significant, in the incidence of subsequent infarction ($x_E^2 = 9.71$; $p < 0.01$) and of cardiac deaths ($x_E^2 = 19.88$; $p < 0.01$) but not of angina or cardiac failure. Angina occurred more or less equally ($x_E^2 = 0.05$; $0.90 > p > 0.80$) and there were slightly more instances of cardiac failure in the long-term group ($x_E^2 = 0.20$; $0.90 > p > 0.80$). In the patients who received anticoagulants during the acute phase only, the incidence of subsequent myocardial infarction was more than three times greater and the number of fatalities of cardiac origin was six times greater than in those who were subsequently maintained on continuous anticoagulant therapy.

Subsequent Cardiac Deaths in Relation to the Previous Incidence of Myocardial Infarction

In view of the difference in incidence of previous coronary artery disease in the two groups, it is important to ascertain whether this difference influenced mortality subsequent to the presenting attack of myocardial infarction in the patients receiving and those not

receiving continuous anticoagulant therapy (table 11).

Of the 41 patients in the entire series with a previous history of infarction, 13 subsequently died (31.7 per cent), whereas of 129 patients without a history of previous infarction 19 eventually died (14.6 per cent). This difference is significant ($X^2_E = 4.91$; $0.05 > p > 0.02$) and indicates that the mortality subsequent to myocardial infarction is greater in those who have suffered previous attacks of infarction. However, when a comparison is made of the relation of previous infarction to subsequent mortality in the long- and short-term groups, it is found that of the 82 patients in the long-term group, 24 had experienced previous myocardial infarction prior to the presenting attack and of these, three (12.5 per cent) died, whereas the remaining 58 patients gave no history of previous infarction, and of these only two (3.4 per cent) died. Of the 88 patients in the short-term group, 17 had experienced previous infarction, and of these 10 (58.8 per cent) died, whereas of the 71 with no history of previous infarction, 17 (29.9 per cent) died. These results show that whether or not the patients receive continuous anticoagulant therapy the subsequent mortality is significantly greater in those who have suffered previous attacks of myocardial infarction ($x^2_E = 4.91$; $0.05 > p > 0.02$). However, the numbers of fatalities are far less in those receiving continuous anticoagulant therapy ($x^2_E = 7.84$; $p < 0.01$). In fact, from these results it appears that a fatal outcome was no more likely to occur in the patients with a previous history of infarction later receiving anticoagulants, than in those without previous infarction not receiving this treatment ($x^2_E = 0.81$; $0.50 > p > 0.30$), indicating that long-term anticoagulant therapy has improved the prognosis of those who have had previous infarcts, at least to the level of those with no previous infarcts.

TABLE 11.—*Subsequent Cardiac Deaths in Relation to Previous Incidence of Myocardial Infarction*

	Numbers of Cases		
	Total—170	Long Term—82	Short Term—88
Previous infarction	41	24	17
Subsequent deaths	13 (31.7%)	3 (12.5%)	10 (58.8%)
No previous infarction	129	58	71
Subsequent deaths	19 (14.6%)	2 (3.4%)	17 (29.9%)

TABLE 12.—*Subsequent Cardiac Deaths in Relation to Previous Incidence of Myocardial Infarction in the Severe Cases*

	Numbers of Cases		
	Total—127	Long Term—67	Short Term—60
Previous infarction	36	21	15
Deaths	13 (36.1%)	3 (14.3%)	10 (66.6%)
No previous infarction	91	46	45
Deaths	18 (19.8%)	2 (4.3%)	16 (35.5%)

When the mild cases are again excluded and a comparison is made of only the severe cases, the difference in mortality between long- and short-term treated patients becomes even more striking. Of particular importance (table 12) is the high mortality (66.6 per cent) observed subsequent to recovery from a severe presenting myocardial infarct in the group with a history of previous infarction not receiving anticoagulants continuously and the small number of fatalities (14.3 per cent) in a similar group maintained on this treatment. It would appear that patients falling into this category are those most in need of preventive anticoagulant therapy.

Subsequent Cardiac Deaths in Relation to the Previous Incidence of Angina Pectoris Not Due to Myocardial Infarction

Since it has been pointed out that the absence of a history of angina prior to an attack of myocardial infarction may influence adversely the subsequent prognosis,[8] it is necessary to test whether the relative incidence of previous angina in the two groups may have been a factor in determining the differences observed in the subsequent mortality. Table 13 shows the incidence of previous angina in relation to subsequent deaths of cardiac origin

in 129 patients who had not suffered from previous myocardial infarction. Thirty-one patients had experienced previous angina of whom three subsequently died (9.7 per cent) and 98 patients had had no angina and of these 16 subsequently died (16.3 per cent) ($x_E^2 = 0.38$; $0.70 > p > 0.50$). Table 13 also shows that in the long-term group of 58 patients who had not suffered from previous infarction, 19 had experienced previous angina and of these none died, whereas 39 had had no angina, and of these two died (5.1 per cent).

In the short-term group, 71 patients had had no previous infarction and of these 12 had experienced previous angina, with three subsequent deaths (25 per cent) while 59 had had no angina with 14 subsequent deaths (23.7 per cent). As the mortality rates for the series as a whole and for each group separately do not differ materially, it is apparent that the presence or absence of previous angina did not influence the prognosis subsequent to an attack of myocardial infarction.

In a comparison of the subsequent mortality in relation to the incidence of previous angina in the long- and short-term groups, it is apparent that a greater number of fatalities occurred in the patients not receiving continuous anticoagulant therapy. The difference in respect of the patients without previous coronary artery disease is statistically significant ($x_E^2 = 4.53$; $0.05 > p > 0.02$), but in regard to those with previous angina, the numbers are too small for accurate computation, although the tendency is in favor of the patients receiving anticoagulant therapy.

TABLE 13.—*Subsequent Cardiac Deaths in Relation to Previous Incidence of Angina Pectoris not due to Infarction*

	Numbers of Cases		
	Total—129	Long Term—58	Short Term—77
Previous angina.	31	19	12
Subsequent deaths.....	3 (9.7%)	0	3 (25.0%)
No previous angina	98	39	59
Subsequent deaths.....	16 (16.3%)	2 (5.1%)	14(23.7%)

DISCUSSION

Anticoagulant therapy on a short-term basis for acute thrombotic states has been extensively used for a number of years. In respect of acute myocardial infarction ample evidence has accrued in support of its beneficial effect[9-13] although dissenting views for its routine use[6,7] or for its use at all[14] have been expressed.

For prophylaxis on a short-term basis anticoagulants have been resorted to in postoperative states.[15,16] On a long-term basis prophylaxis by means of anticoagulants for recurring thromboembolic disease has been used by several workers whose opinions as regards its efficacy and practicability have been uniformly favorable;[17-21] the conditions treated have included recurring thrombophlebitis with or without pulmonary embolism and chronic valvular heart disease associated with embolization.

Several reports have appeared concerning long-term anticoagulant therapy on a prophylactic basis for patients who have experienced one or more attacks of myocardial infarction and also for those suffering from angina pectoris. In anticipation of this therapeutic approach, a statement made by Wright in 1947[22] is of interest. It reads: "Another investigation that should be undertaken is the follow-up observation of patients who have received anticoagulant therapy and have thus survived one attack. Their outlook for the future should be evaluated. A follow-up study should be undertaken of individuals who can continue Dicumarol therapy over a long period of time in order to determine whether their prognosis is thereby improved, as compared with individuals who are not able to continue long-term Dicumarol therapy".

The first published report was made by Nichol and Fassett[23] who, in an attempt to forestall acute coronary thrombosis, treated five patients with Dicumarol continuously for periods ranging from 6 to 32 months. Subsequently a number of reports[24-36] have appeared from different medical centers, the most recent communication being that of Nichol and his associates[37] who carried out a

cooperative study in which approximately 1,100 patients with myocardial infarction or coronary insufficiency were treated with oral anticoagulants for six months to eight years. While on the regimen, 16 per cent died, but autopsy seldom showed fresh transmural infarction. In 54 per cent of the cases, the treatment was continuous. These authors concluded that the use of long-term anticoagulants probably prevented recurrent infarction and prolonged life in many patients, judging by comparison with a control group of 500 patients.

Although the general concensus of opinion concerning the value of this therapeutic regime is favorable, it must be emphasized that in none of the reported series has due consideration been given to the previous history of coronary artery disease or to the degree of severity of the presenting attack of infarction. Furthermore, in the majority of reports the period of observation has been relatively short and a comparable control series of cases observed parallel in time has not been studied.

The results of our series indicate that in mild or uncomplicated cases, whether under treatment or not, the ultimate outlook is favorable, in sharp contrast to the substantial mortality rate found in severe or complicated cases.

It is obvious, therefore, that in an evaluation of the natural history of this disease or of any therapeutic regimen, due consideration must be given to the degree of severity of the presenting attack and thus the average survival times hitherto reported for several series of patients must be reconsidered in this light. In a recently reported series of patients who recovered from the acute phase of their first infarct, the average survival time was as long as eight years, but this figure is given irrespective of the degree of severity of the attack. In view of the wide variation in survival time for patients who have recovered from acute myocardial infarction, the prophylactic value of anticoagulant therapy can only be determined by a study of a substantial number of patients followed long enough to bear comparison with the observed survival times in this disease.

In the present study a highly significant difference has been noted in a comparison of those receiving and those not receiving anticoagulants in respect not only of the mortality (7.3 per cent and 33 per cent) but also of the recurrence rate of infarction (8.5 per cent and 27.3 per cent). Despite the fact that the differences in regard to recurrence of infarction and to mortality are statistically significant, these results are presented with reservation. It is realized that because the conditions of management of the patients of the two groups following the presenting attack of myocardial infarction were not exactly similar and therefore not strictly comparable, these differences may not be due entirely to the anticoagulant therapy.

The patients receiving long-term therapy attended the clinic or laboratory at regular intervals for prothrombin tests. Under close medical supervision, signs or impending complications were more likely to have been detected in time, ensuring the early institution of appropriate treatment; furthermore, these patients would have had the benefit of advice about their mode of living and any problems arising in their life situation. Sensing an element of protection and security, in the belief that under this medication thrombosis was less likely to occur, as well as the reassurance gained by constant medical supervision may have been factors in allaying the apprehension and fear for the future which so often troubles patients who have experienced one or more attacks of coronary thrombosis. The patients receiving continuous anticoagulant therapy often displayed much interest in the treatment and in their state of health, and it has been argued that this undue concern may act deleteriously by disturbing the patient's peace of mind, particularly when wide fluctuations of the prothrombin level are encountered. We have observed, however, that this is the exception and that by and large these patients are not unduly disturbed but tend rather to display optimism and a sense of security while under this regimen. There are observers[38-41] who emphasize the importance of the role that stressful emotional factors may play in the pathogenesis of intravascular thrombosis, so that it is not beyond the realm of possibility

that constant reassurance may have influenced the result of this clinical study.

On the other hand, the incidence of complications will have been more accurately recorded in the patients under close medical supervision than in those examined at infrequent intervals. In the latter patients, symptoms and episodes due to recurrences of coronary artery disease may not have been reported by the patient or his family physician or may have escaped recognition and thus will not have been documented. The true incidence of complications in the short-term group is therefore likely to be higher than that recorded. The influence of constant medical supervision and other undetermined circumstances on the ultimate prognosis of myocardial infarction could the better be judged by the "double-blind placebo" method of clinical trial, but it is unlikely that the observed differences between the two groups can be attributed solely to these factors and it is reasonable to assume that the prolonged use of anticoagulant drugs actually exerted an effect on the circulating blood which prevented intravascular thrombus formation or beneficially influenced the coronary circulation by some mechanism as yet undetermined. That this is possibly true is supported by the recent observations of Sise,[42] who reported that when phenylindandione is administered continuously for periods longer than three weeks, it exerts a true anticoagulant effect by increasing the clotting time, as measured not only by the usual method in glassware, but also by noting the clotting time of blood flowing through a needle inserted in a vein obstructed by a tourniquet at a pressure of 50 mm. Hg. The increase in clotting time is attributed by this worker to a reduction of plasma thromboplastin component (PTC) which does not occur until the drug has been given for a period of approximately three weeks but persists for as long as the drug is administered. A similar action of the oral anticoagulants when given to patients for prolonged periods has been noted by Connell[43] who finds it sufficient to regulate the dosage of the drug by means of the clotting time of the blood rather than by its prothrombin content. These aspects of the problem have recently been discussed by Hunter,[44] who suggested that doses of coumarin anticoagulants much smaller than those in use at present, may prove to be effective by lowering the blood thromboplastin level without the danger of bleeding. The absence of a true anticoagulant effect with Dicumarol when given for short periods may explain why the difference between the treated and untreated cases on a short-term basis is not as striking as that observed on a long-term basis. The alleged superiority of heparin over the oral anticoagulants in the treatment of acute thrombotic states may possibly also be explained in this way.

Summary and Conclusions

Two hundred eight patients with myocardial infarction having received anticoagulant therapy during the acute phase and having survived for three months or more, were observed 3 to 76 months until death or the end of the present study (Sept. 1, 1953). Those patients treated for three months or longer comprise the long-term group while those treated for less than three months comprise the short-term control group. One hundred twenty patients were treated for three months or longer but 38 of them who discontinued treatment after this period of time or who were treated intermittently have been excluded from the comparative study.

The long and short-term groups are compared in respect of mortality, incidence of recurrent infarction, angina and cardiac failure.

Of the 82 patients who constitute the long-term group the mortality rate is 7.3 per cent and there have been seven recurrences of myocardial infarction, whereas of the 88 patients in the short-term group the mortality rate is 33 per cent and there have been 24 recurrences.

Separate comparisons are made of mild and severe cases, and when the former are eliminated, the mortality rate in the long-term group, which now comprises 67 patients, is 9 per cent with seven recurrences of infarction, whereas in the short-term group totalling 60 patients it is 46.7 per cent with 21 recurrences.

Of the severe cases with a history of previous infarction, the mortality rate in the long-term group (21 cases) is 14.3 per cent compared

with 66.6 per cent for the short-term group (15 cases).

The incidence of angina following the presenting attack of myocardial infarction is approximately the same for both groups, whereas relief or improvement of this condition occurred in 56 per cent of the long-term group and in 23 per cent of the short-term group.

During the course of the study cardiac failure occurred with similar frequency in both groups but the mortality associated with this complication was 11.8 per cent in the long-term group compared with 57.1 per cent in the short-term group.

From this study it would appear that patients in whom the presenting attack is mild in addition to being the first one, and who receive short-term anticoagulant therapy, show a favorable outlook in respect of subsequent infarction, cardiac failure and death, irrespective of whether or not the anticoagulant therapy is continued indefinitely. By contrast, the patients most likely to benefit from long-term anticoagulant therapy are those in whom not only is the presenting attack severe but there is also a history of previous myocardial infarction.

Summario in Interlingua

Un gruppo de 208 patientes con infarctos myocardiac, qui habeva recipite anticoagulantes durante le phase acute de lor morbo e qui habeva supervivite pro al minus 3 menses, esseva observate durante periodos de inter 3 e 76 menses usque al tempore de lor morte o usque al fin del presente studio (1 de septembre 1953). Patientes tractate durante 3 menses o plus forma le "gruppo a longe durantia." Illes tractate durante minus que 3 menses forma le "gruppo de controlo a breve durantia." Un total de 120 patientes esseva tractate durante 3 menses o plus; sed 38 de illes esseva excludite del presente studio comparative proque lor tractamento esseva interrumpite post le fin del 3 menses o proque le tractamento in lor casos esseva intermittente.

Nos ha comparate le gruppo a longe durantia con le gruppo a breve durantia quanto al mortalitate, frequentia del recurrentia de infarctos, angina, e dysfunctionamento cardiac.

Inter le 82 patientes del gruppo a longe durantia le mortalitate esseva 7,3 pro cento. In iste gruppo il habeva 7 recurrentias de infarcimento myocardiac. Inter le 88 patientes del gruppo a breve durantia le mortalitate esseva 33 pro cento. Il habeva in iste gruppo 24 recurrentias.

Nos ha comparate separatemente le gruppos de leve e sever casos. Post excluder le leve casos nos obteneva un gruppo a longe durantia consistente de 67 patientes. Le mortalitate in iste gruppo esseva 9 pro cento. Il habeva in illo 7 recurrentias. Le gruppo a breve durantia se reduceva a 60 patientes con un mortalitate de 46,7 pro cento e 21 recurrentias.

Inter le casos sever con un historia de previe infarcimento, le mortalitate del gruppo a longe durantia, que consisteva de 21 casos, esseva 14,3 pro cento. Le correspondente gruppo a breve durantia consisteva de 15 casos e rendeva un mortalitate de 66,6 pro cento.

Le frequentia de angina post le attacco hospitalisante esseva proximemente le mesme in ambe gruppos, sed alleviamento o melioration de iste condition occurreva in 56 pro cento del casos in le gruppo a longe durantia e in 23 pro cento del casos in le gruppo a breve durantia.

In le curso del studio, dysfunctionamento cardiac occurreva con simile frequentias in ambe gruppos, sed le mortalitate associate con iste complication amontava a 11,8 pro cento in le gruppo a longe durantia, comparate con 57,1 pro cento in le gruppo a breve durantia.

Le presente studio permitte le conclusion que in le caso de patientes in qui le attacco hospitalisante es non solo leve sed etiam le prime e in qui un therapia anticoagulante a breve durantia es utilisate, le prognose es favorabile in relation a subsequente infarctos, dysfunctionamento cardiac, e morte—sin reguardo a si o non le therapia anticoagulante es continuate indefinitemente. Per contrasto, le patientes profitante le plus probabilemente ab un therapia anticoagulante a longe durantia es le patients in qui le attacco hospitalisante es sever e in qui infarctos myocardiac ha occurrite previemente.

REFERENCES

[1] Duguid, J. B.: Thrombosis as a factor in the pathogenesis of coronary atherosclerosis. J. Path. & Bact. **58:** 207, 1946.

[2] —: Pathogenesis of atherosclerosis. Lancet **2:** 925, 1949.

[3] —: The Arterial Lining. Lancet **2:** 207, 1952.

[4] —: Diet and Coronary Disease. Lancet **1:** 891, 1954.

[5] Stein, H. B. and Wallace, B. V.: The prothrombin level in patients on Dicumarol therapy: A simplified capillary technique. South African M. J. **26:** 353, 1952.

[6] Russek, H. I. and Zohman, B. L.: "Selective" versus "routine" use of anticoagulants in acute myocardial infarction. J.A.M.A. **156:** 1130, 1954.

[7] Schnur, S.: The current dispute concerning anticoagulants in acute myocardial infarction. J.A.M.A. **156:** 1127, 1954.

[8] Cole, D. R., Singian, E. B. and Katz, L. N.: The long-term prognosis following myocardial infarction and some factors which affect it. Circulation **9:** 321, 1954.

[9] Wright, I. S.: Experiences with Dicumarol in the treatment of coronary thrombosis. Proc. Am. Federation Clin. Res. **2:** 101, 1945.

[10] Nichol, E. S. and Page, S. W., Jr.: Dicumarol therapy in acute coronary thrombosis: results in 50 attacks. J. Florida M. A. **32:** 365, 1946.

[11] Wright, I. S., Marple, C. D. and Beck, D. F.: Report of the committee for the evaluation of anticoagulants in the treatment of coronary thrombosis with myocardial infarction. Am. Heart J. **36:** 801, 1948.

[12] Gilchrist, A. R.: Anticoagulants in coronary occlusion. Proc. Roy. Soc. Med. **47:** 317, 1954.

[13] Wright, I. S., Marple, C. D. and Beck, D. F.: Myocardial infarction; its clinical manifestations and treatment with anticoagulants. A study of 1031 cases. New York, Grune and Stratton, 1954.

[14] Evans, W.: Anticoagulant therapy in Coronary occlusion. Proc. Roy. Soc. Med. **47:** 318, 1954.

[15] Barker, N. W., Cromer, H. E., Hurn, M. and Waugh, J. M.: Use of Dicumarol in the prevention of post-operative thrombosis and embolism with special reference to dosage and safe administration. Surgery **17:** 207, 1945.

[16] Allen, E. V.: The clinical use of anticoagulants: report of treatment with Dicumarol in 1,688 post-operative cases. J.A.M.A. **134:** 323, 1947.

[17] Sprague, H. B. and Jacobsen, R. P.: A case of rheumatic heart disease with periodic arterial embolism: ambulatory treatment with Dicumarol. M. Clin. North America **32:** 1309, 1948.

[18] Hines, E. A., Jr. and Barker, N. W.: Anticoagulant therapy in chronic cardiovascular diseases. M. Clin. North America **33:** 335, 1949.

[19] Cosgriff, S. W.: Prophylaxis of recurrent embolism of intracardiac origin. Protracted anticoagulant therapy on an ambulatory basis. J.A.M.A. **143:** 870, 1950.

[20] Askey, J. M. and Cherry, C. B.: Thromboembolism associated with auricular fibrillation. Continuous anticoagulant therapy. J.A.M.A. **144:** 97, 1950.

[21] Bay, E. B., Adams, W. R., Jones, R. J., Page, R. G. and Seide, M.: The use of anticoagulant drugs in ambulatory patients. Circulation **9:** 741, 1954.

[22] Wright, I. S. and Foley, W. T.: Use of anticoagulants in the treatment of heart disease with special reference to coronary thrombosis, rheumatic heart disease with thromboembolic complications and subacute bacterial endocarditis. Am. J. Med. **3:** 718, 1947.

[23] Nichol, E. S. and Fassett, D. W.: An attempt to forestall acute coronary thrombosis. Preliminary note on the continuous use of Dicumarol. South. M. J. **40:** 631, 1947.

[24] Foley, W. T. and Wright, I. S.: Long term anticoagulant therapy for cardiovascular diseases. Am. J. M. Sc. **217:** 136, 1949.

[25] Olwin, J. H.: The control of Dicumarol therapy. Am. J. M. Sc. **217:** 427, 1949.

[26] Rice, R. L., Ackerman, J. S. and Saichek, R.: Long term Dicumarol therapy. Ann. Int. Med. **32:** 735, 1950.

[27] Nichol, E. S. and Borg, J. F.: Long term Dicumarol therapy to prevent recurrent coronary artery thrombosis. Circulation **1:** 1097, 1950.

[28] Hellem, A. J.: The practical administration of long term anticoagulant therapy. Nord. Med. **48:** 1558, 1952.

[29] Lund, E.: Long term Dicumarol therapy in thromboembolic conditions, especially coronary thrombosis. Acta med. scandinav. **146:** 252, 1953.

[30] — Control of anticoagulant therapy. Risk of haemorrhage. Acta med. scandinav., Suppl. 287, **147:** 51, 1953.

[31] Owren, P. A.: Long term Dicumarol therapy in cardiovascular diseases. Acta med. scandinav., Suppl. 287, **147:** 46, 1953.

[32] Goldberg, B. and Suzman, M. M.: Long-term anticoagulant therapy in myocardial infarction: A preliminary report. South African M. J. **27:** 389, 1953.

[33] Keyes, J. W., Drake, E. H., James, T. N. and Smith, F. J.: Survival rates after myocardial infarctions with and without long term anticoagulant therapy. Am. J. M. Sc. **226:** 607, 1953.

[34] Nichol, E. S., Phillips, W. C. and Jenkins, V. E.: Anticoagulants in coronary heart disease. M. Clin. North America **38:** 399, 1954.

[35] Tulloch, J. and Wright, I. S.: Long term anticoagulant therapy: further experiences. Circulation **9:** 823, 1954.

[36] OWREN, P.: Long-term anticoagulant therapy in coronary artery disease. Schweiz med. Wchnschr. **84:** 822, 1954.

[37] NICHOL, E. S. et al.: Long term anticoagulant therapy in coronary atherosclerosis: A cooperative study. Presented at the Second World Congress of Cardiology, Washington, D. C. Sept. 12–17, 1954.

[38] CANNON, W. B. AND MENDENHALL, W. L.: Factors affecting coagulation time of blood: IV. Hastening of coagulation in pain and emotional excitement. Am. J. Physiol. **34:** 251, 1914.

[39] MACHT, D. I. AND HOFFMASTER, T.: Physiological, pharmacological and biochemical studies on blood of animals in rage. Fed. Proc. **8:** 102, 1949.

[40] SCHNEIDER, R. A.: Relation of stress to clotting time, relative viscosity and certain other biophysical alterations of the blood in normotensive and hypertensive subjects. A. Research Nerv. & Ment. Dis., Proc. **29:** 818, 1950.

[41] MACHT, D. I.: Influence of some drugs and of emotions on blood coagulation. J.A.M.A. **148:** 265, 1952.

[42] SISE, H. S.: Methods and concepts pertaining to prothrombopenic anticoagulants. Proceedings of the New England Cardiovascular Society, Boston, 1953–1954.

[43] CONNELL, W. F.: Personal communication.

[44] HUNTER, R. B. AND WALKER, W.: The control of anticoagulant therapy in myocardial infarction. Brit. M. J. **2:** 197, 1954.

Inositol and Mannitol Hexanitrates in Hypertension Management

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This clinical study was undertaken because the clinical literature dealing with the use of mannitol and inositol hexanitrate and to a large extent other nitrites and nitrates which have been used in the management of hypertension fails to consider the development of tolerance. It was found that tolerance to the vasodilator action of mannitol and inositol nitrate develops in from 8 to 14 days and is lost completely within 10 days after withdrawal of the drug. The use of these nitrates should be carefully individualized by determining the optimal dose and the period required for the development and loss of tolerance.

QUICKLY acting nitrites and nitrates have been used for decades for the relief of angina pectoris. By physiological methods it can be demonstrated that these drugs increase coronary blood flow provided the blood pressure is not reduced too much by a too large dose of the drug and the coronary vessels have not lost their capacity to dilate.

The more slowly acting nitrites and nitrates, especially the organic nitrates, have been and still are used extensively in the management of hypertension. They have been and are used more or less continuously to reduce the blood pressure on the assumption (A) that the hypertension is due to excessive peripheral vasoconstriction, some of which at least may be counteracted by the vasodilator effect of these compounds, and (B) that they are symptomatically beneficial.

This study was undertaken primarily (1) to determine the blood-pressure reducing effectiveness of a new compound, inositol hexanitrate and (2) of an old compound, mannitol hexanitrate, and (3) to ascertain if tolerance developes to the blood-pressure reducing effects of these two compounds. Because tolerance might develop, the study was not designed to examine critically the clinical effectiveness of the drugs or the best way to administer the drugs so as to avoid the development of tolerance, and in that way really test the value of these long-acting nitrates in the management of the hypertensive patient on the basis of the assumption that a reduction of blood pressure is symptomatically and prophylactically valuable. The clinician (L. B.) giving the medication, including a placebo, and supervising the patients did not know the entire purpose of the study and did not know the identity of the tablets.

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LITERATURE

We have been unable to find in the literature a carefully designed study to test the assumption that a reduction of blood pressure in the hypertensive patient by the use of nitrites or nitrates is symptomatically and prophylactically valuable. This is primarily because no clinical investigator has considered adequately the development of tolerance to the blood-pressure reducing effects of the compound they used. This has occurred, even though some textbooks of pharmacology,[1] have since 1917, pointed out that tolerance to the blood-pressure reducing effects of nitrites and nitrates appears in a few days, is well-established in two to three weeks and that cessation for several days invariably re-establishes the original extent of susceptibility.[2]

Tolerance to nitroglycerine was apparently first observed in 1888.[3] As early as 1898, Laws[4] described the development of tolerance among the employees of the manufacturers of nitroglycerine. It was referred to again in the American literature in 1905.[5, 6] In 1909, Mathew[7] published a well conceived study of the blood-pressure reducing effects of several nitrites and nitrates in patients with hypertension. He found that on repeated use tolerance to nitroglycerine developes in 24 hours, to sodium nitrite (0.12 to 0.2 Gm., three times a day) partially in two weeks. He failed to observe tolerance to erythrol nitrate (0.06 Gm., three times a day) and to mannitol hexanitrate (0.06 Gm., three times a day) when prescribed for long periods. Wallace and Ringer,[8] who carefully

studied the blood-pressure reducing effects of several nitrites and nitrates, as regards latent period of action, extent and duration of the decrease in blood pressure, did not study tolerance (for a table giving such data see references 1 and 9). A number of clinicians prior to 1915 reported on the use of nitrites in the management of hypertension without mentioning the subject of tolerance.[10, 11]

During World War I, attention was again directed to the tolerance developed by persons making nitroglycerin.[12, 13] (Some munition workers develop a tolerance readily and others do not; the latter usually discontinue such work.) But, prior to 1929 a carefully controlled study of the tolerance and cross tolerance to nitrites and nitrates had not been conducted. Then, Meyers and Austin[14] found that rabbits developed within several days a definite tolerance to the blood-pressure reducing effects of sodium nitrite with a cross-tolerance to nitroglycerin. Crandall[15b] found that dogs made tolerant to amyl nitrite are tolerant to the vascular effects of sodium nitrite. Crandall, Leake, Loevenhart, and Muehlberger[15a] using normal human subjects found that a tolerance to the headache-producing effect of the nitrites and nitrates developed faster than to the blood-pressure reducing effect. The ease of developing some tolerance to one headache dose ranked in order as follows: amyl nitrite (2 to 3 hours), methyl nitrate (24 hours), ethylene glycol dinitrate (32 hours), glycerol trinitrate (38 hours), and erythrol tetranitrate (60 hours). Cross tolerance was demonstrated. They failed to observe the development of tolerance to the vascular effects of sodium nitrite (0.22 Gm. two times a day) in four days in man and in six days in a dog (0.3 Gm., two or three times per day). In two subjects, however, tolerance to the vascular effects of sodium nitrite were abolished by rendering them tolerant to ethylene glycol dinitrate.

Since 1924, 11[9, 16-26] monographs or textbooks, and ten[27-36] articles dealing with the treatment of hypertension reviewed by us do not mention the possibility of tolerance developing, and in that way annulling the potential benefit of the prolonged use of nitrites and nitrates. One author[37] of a pedagogical article mentions the possibility of tolerance developing to all nitrites and nitrates as the subject is presented in textbooks of pharmacology.[1, 2]

The literature clearly establishes that adequate doses of the nitrites or nitrates usually employed therapeutically reduce blood pressure of normal subjects, the extent depending on the dose and the susceptibility of the subject.[1, 2, 7, 8, 14, 15] The susceptibility of patients with hypertension varies widely.[7, 8, 11, 29, 30, 34, 36, 38] Some patients are very sensitive, and collapse or a postural hypotension may occur.[29, 30] In such patients the action of the drug is primarily on the venous side causing a pooling of the blood in the veins, a decreased cardiac output, and an increase in central vasoconstrictor tone.[39] In some patients there is no change or there may even be a rise in blood pressure[34] with ordinary doses. The effect on urinary output also varies widely in different patients.[11, 27, 34, 39]

Therapeutically there is no evidence indicating that the daily use of the nitrites or nitrates modifies the course of hypertensive disease. Except for the benefit derived from the cautious use of the quickly and short-acting nitrites and nitrates for the relief of angina pectoris, most authors today either are skeptical regarding, or deny, their value in the management of the symptoms of hypertension. This is the view which would logically develop in the case that tolerance developed within a week or two after starting a slow acting drug. A drug such as bismuth subnitrate could at first give some symptomatic relief due to a small blood pressure decreasing effect which could then be continued as a psychotherapeutic effect after the development of tolerance. Thus, one observer could report an improvement[31] and other observers could report that the compound had no more effect than a placebo or frequent office calls.[32, 33, 34]

Regarding mannitol hexanitrate, Mathew[7] wrote: "With it I have not observed the same individual susceptibility or any tendency to unpleasant effects, probably owing to the fact that it produces its maximum effect much more slowly than erythrol." He advised that the dose should be individualized by determining the dose which lowers blood pressure without causing undesirable symptoms. He observed no evidence of tolerance, though one cannot be certain from his article how carefully he checked to ascertain how regularly his patients took the drug. Evans and Loughman[34] reported that the use of mannitol hexanitrate had no greater beneficial effect than a placebo. However, their patients reported to them only every two weeks, and hence the development of a tolerance may have been overlooked. Weaver, Wills, and Hodge[35] studied 19 hypertensive patients, eight of whom received mannitol hexanitrate (30 mg., three times per day) and 11 a control placebo. Side effects were not seen in 28 patients receiving the 30-mg. dose for varying periods of time. The placebo therapy did not produce symptomatic relief similar to that obtained with the drug. These observers, however, reported that the symptomatic relief occurred without a fall in blood pressure. (A) Does this mean that relief was obtained for a few days due to the vascular effect of the drug and that, then, a tolerance developed and a psychotherapeutic effect appeared? (B) Or, does it mean that relief may actually be obtained without a lowering of blood pressure as occurs sometimes in angina pectoris after taking nitroglycerin or amylnitrite?[17]

A 30 to 60-mg. dose of mannitol hexanitrate orally starts to lower blood pressure after a latent period of 15 to 30 minutes; produces a fall in systolic pressure of from 10 to 50 mm. Hg, which becomes maximum in from 60 to 120 minutes; and

disappears in from four to six hours.[7, 35] It increases coronary flow in the perfused rabbit's heart.[40] There are no reports published to our knowledge on the effect of inositol hexanitrate on blood pressure.

This review indicates that further evidence on the development of tolerance to the slow-acting nitrates and nitrites is needed, and that a study of their symptomatic effectiveness in which the factor of tolerance, as well as psychotherapeutic effects, is considered has not been performed.

Experimental Design

All the 32 hypertensive patients were ambulatory and for the most part asymptomatic. Such patients were selected because the objectives of the investigation were to test the hypotensive action of a new organic nitrate and to ascertain whether tolerance developed to mannitol hexanitrate and the new nitrate, inositol hexanitrate.

To exclude patients with other diseases, a complete history and physical examination as well as the following laboratory tests were performed: a complete blood cell and hemoglobin study; serology; urinalysis; blood plasma nonprotein nitrogen; renal urea clearance and/or concentration-dilution test; electrocardiogram, 12 leads; and chest x-ray films.

All subjects had urea clearances greater than 55 per cent of normal, or had urine concentrations greater than 1.022. Cardiac enlargement was present in 16 patients; dilation and tortuosity of the aorta in five; and cardiac enlargement and aortic dilatation in four. Seven patients had normal sized hearts; 12 had normal electrocardiograms. Of the 20 patients with abnormal electrocardiograms, 10 showed left ventricular hypertrophy and/or strain patterns; eight showed nonspecific abnormal patterns; and two right bundle branch block patterns. Additional laboratory tests were performed on individual patients when indicated to investigate complaints not related to hypertension.

In order to avoid completely all prejudice, a "blind-placebo plan" of study was undertaken. At no time in the study did the clinical investigator know the identity of the three tablets used. He was instructed to give the three tablets to alternate patients as they became a member of the study group and to make certain observations with the objective that after several months the observations would show a difference or similarity in the action of the three tablets.

At each visit, the patient sat in a waiting room for approximately 30 minutes before entering the consultation room. The subjective complaints were discussed and recorded. The blood pressure was then determined to the nearest 5 mm. Hg mark in sitting, supine, and standing positions in the left arm and then on the right arm. In this report the pressure taken in the right arm in sitting position was arbitrarily chosen for comparisons. Thus, the value used was one which in all subjects followed sitting in the waiting room and the same changes of position during three blood pressure determinations.

The tablets were labeled X, Y, and Z. They contained respectively 30 mg. mannitol hexanitrate, placebo, and 10 mg. inositol hexanitrate. The dose was increased by changing the number of tablets taken.

Analyses of the data were performed by the analysis of variance technic.[41]

Other details of the procedure will be given under the results.

Observations

Part I. On the basis of blood pressure and clinical response can one in a "blind" or "unknown" test differentiate between the results with a placebo tablet and tablets containing a slow acting nitrate?

Procedure: After two control visits and blood pressure determinations, the patients alternately were first placed on tablet X, or Y, or Z, and were instructed to take two tablets four times daily or every four hours while awake. On the next visit, two weeks later, the patient returned the unused portion of his initial medication to make certain that the directions had been followed, and a supply of a second medication was given. These medications were given in random sequence to each patient, allowing each patient to serve as his own control. Thus, the patient was rotated from tablet X to Y, to Z, etc. In this way, the results on those patients who left the study group after a few months were still of value, since observations on the effect of each medication on them had been made. Those patients who continued in the group had several observations on each medication. In general, after two weeks on each of the three tablets, the patients were rotated on each medication for four weeks, then rotated on each at higher doses. This procedure excluded variations in blood pressure and symptoms due to changes of season. The general effects of temperature, barometric pressure, humidity, snow, rain, and any number of subtle and unknown factors on blood pressure were nullified by the fact that on any given clinic day different patients were given different medications; that is, during any single period some patients were taking tablet X, others tablet Y, and still others tablet Z.

Results: In our tables and statistical analyses the number of blood pressure determinations was the same for each medication. Since the initial dosage level was two tablets, and then the number of tablets was increased in order to attempt to obtain a greater effect on the patient's blood pressure level, several dosage levels were used. To simplify the presentation

and analysis of the data, the doses on all the patients were arbitrarily divided into two groups, namely, a "low dosage group" (two to six tablets four times daily) and a "high dosage group" (9 to 12 tablets four times daily).

In the "low dosage group", there were 130 complete series of determinations on each of the three tablets on 32 patients. The mean systolic pressures in mm. Hg for the three tablets were: X = 198.3; Y = 197.3; and Z = 198.4; the respective mean diastolic pressures being 111.1, 110.7, and 111.2. There obviously is no statistically significant difference in these pressures (tables 1 and 2). *Since we know (vide infra) that the two nitrates on a single administration in the range used causes a fall in blood pressure, the failure to find a fall can only be due to the development of tolerance.*

In the "high dosage group" there were 59 complete series of determinations on 16 patients. The mean systolic pressures in mm. Hg for the three tablets were: X = 198.5; Y = 206.6; and Z = 202.3; the respective mean diastolic pressures were 111.3, 115.2, and 113.8. The differences between the systolic and diastolic pressures in the determinations made while on the nitrites were significantly lower (tables 3 and 4). Though the differences are statistically significant, they would not appear to be clinically significant because they are relatively so small. Again the existence of tolerance is evident, in view of the huge doses administered.

Comment: This evidence demonstrates why some investigators have obtained the same

TABLE 1.—*The Relationship of Systolic Pressure to "Low" Doses of Tablets X (Mannitol Hexanitrate), Y (Placebo), and Z (Inositol Hexanitrate)*

Analysis of Variance

Variance source	Degrees of freedom	Sums of squares	Mean square	F
Between patients	31	257,350	8,301.6	36.7
Between treatments	2	105	52.5	.2
Residual error	356	80,485	226.1	
Total	389	337,940		

There are no significant differences between the means of the systolic pressures while on the three different medications.

TABLE 2.—*The Relationship of Diastolic Pressure to "Low" Doses of Tablets X (Mannitol hexanitrate), Y (Placebo), and Z (Inositol Hexanitrate)*

Analysis of Variance

Variance source	Degrees of freedon	Sums of squares	Mean squares	F
Between patients	31	73,305	2,364.7	44.3
Between treatments	2	21	10.5	.2
Residual error	356	19,024	53.4	
Total	389	92,350		

There are no significant differences between the means of the diastolic pressures while on the three different medications.

TABLE 3.—*The Relationship of Systolic Pressure to "High" Doses of Tablets X (Mannitol Hexanitrate), Y (Placebo), and Z (Inositol Hexanitrate)*

Analysis of Variance

Variance source	Degrees of freedom	Sums of squares	Mean squares	F
Between patients	15	106,574	7,105	29.9
Between Y and (X + Z)	1	1,526	1,526	6.4
Between X and Z	1	429	429	1.8
Residual error	159	37,802	238	
Total	176	146,331		

The systolic pressure was significantly lower on (mannitol plus inositol hexanitrate) treatments than on placebo treatment ($p < .01$). There was no significant difference between the systolic pressures on the mannitol and inositol hexanitrates.

TABLE 4.—*The Relationship of Diastolic Pressure to "High" Doses of Tablets X (Mannitol Hexanitrate), Y (Placebo), and Z (Inolsito Hexanitrate)*

Analysis of Variance

Variance source	Degrees of freedom	Sums of squares	Mean squares	F
Between patients	15	30,873	2,058	36.1
Between Y and (X + Z)	1	1,397	1,397	24.5
Between X and Z	1	204	204	3.58
Residual error	159	9,033	57	
Total	176	41,507		

The diastolic pressure was significantly lower on (mannitol plus inositol hexanitrate) treatments than on placebo treatment ($p < .001$). There was no significant difference between the diastolic pressures on the mannitol and inositol hexanitrate treatments.

effects on the blood pressure of hypertensive patients on repeated daily use of the nitrites or nitrates as those obtained with a placebo. Apparently those who have failed to observe tolerance develop when these organic nitrites were used did not control their patients adequately so that the medication was taken sufficiently regularly to cause the development of tolerance.

In order to test this interpretation of the foregoing observations two other series of experiments were performed.

Part II. What is the effect on blood pressure of mannitol and inositol hexanitrate when given in a single dose?

Procedure: Six of our hypertensive patients whose blood pressure had been found repeatedly not to be lowered by relatively huge doses of mannitol and inositol hexanitrate were used in this experiment. Before using them all nitrate medication was discontinued for four weeks. Then, rotating at two week intervals a single dose of 12 tablets of mannitol (0.36 Gm.) and inositol (0.12 Gm.) hexanitrate and placebo were administered to each subject. The blood pressure was then determined at intervals up to four and one-half hours.

Results: The results, as averages, are graphed in figure 1. It will be noted that the placebo had no effect over a period of four and one half hours. The mannitol (0.36 Gm.) produced a marked fall in systolic (64 mm. Hg) and diastolic (32 mm. Hg) pressure which had not returned to the control pressure after four and one half hours. The inositol (0.12 Gm) produced a decided fall in systolic (44 mm. Hg) and diastolic (20 mm. Hg) pressure which had not returned to the control pressure after four and one half hours.

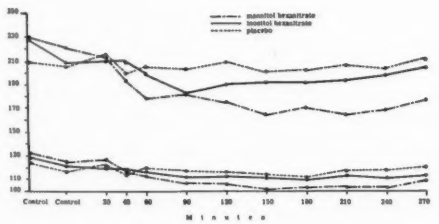

FIG. 1. Showing the response of the systolic and diastolic blood pressure of hypertensive patients to a placebo and to mannitol and inositol hexanitrate.

Part III. What period of time is required to produce tolerance to mannitol and inositol hexanitrate?

Procedure: Fifteen hypertensive patients served as subjects. They were divided into two groups. One group consisted of eight patients whose systolic and diastolic blood pressures were greater than 150 and 100 mm. Hg, respectively. The second group consisted of seven patients whose systolic and diastolic pressures were under 150 and 100 mm. Hg, respectively.

Each patient was given a single dose of 12 tablets of each medication and the blood pressure was determined for a period of four hours. Twelve tablets four times per day were then administered, five of the 15 patients receiving tablet X, five tablet Y, and five tablet Z. The blood pressure of each of the 15 patients was taken on the second, third, fourth, sixth, and eighth days. The medication was then stopped for two weeks. Then the patients were given a new tablet. This was repeated until each of the 15 patients had received each tablet for a period of eight days, each period being broken by a two-week period of no medication.

Results: Reference to figure 2 shows the averaged results on the first group of 8 patients. Figure 3 shows the results on the second group of seven patients.

In the first group (fig. 3), it will be noted the tolerance to mannitol and inositol developed in eight days. In the second group, the results with inositol were variable, but tolerance to the mannitol was present but not complete at eight days.

The tolerance is apparently completely absent after discontinuing the drugs for 14 days. In a few patients who had neglected, we found, to take their medication for 10 days, tolerance had been completely lost.

Side Reactions: Side reactions, such as headaches, dizziness and palpitation, occurred when the dosage level was suddenly increased above the level of the tolerance which had been developed. In those cases where a small dose such as 60 mg. four times daily, was given and slowly increased to 0.4 Gm. of mannitol four times daily, there were no symptoms or the symptoms were minimal. A few patients were apparently unable in a period of one month to develop a complete tolerance to 0.4 Gm. of mannitol four times per day. Some patients who had not developed a tolerance to the

FIG. 2. Showing the development of tolerance to mannitol and inositol hexanitrate in eight patients whose systolic and diastolic blood pressures were greater than 150 and 100 mm. Hg, respectively.

FIG. 3. Showing the development of tolerance to mannitol and inositol hexanitrate in seven patients whose systolic and diastolic pressures were under 150 and 100 mm. Hg, respectively.

larger doses, developed mild anorexia; one such patients developed "bloating". One patient regularly, and two other patients occasionally, developed ventricular ectopic beats when taking 0.4 Gm. of mannitol hexanitrate. One patient developed an erythematous, papular, pruritic skin eruption involving the arms and hands while taking 0.28 Gm. of mannitol hexanitrate four times per day. The eruption subsided completely within one week after termination of the medication. Another patient complained of a transient pruritus of the arms while taking 60 mg. of inositol hexanitrate.

Angina: In three patients who had frequent attacks of angina the frequency of the attacks was not affected, as might be anticipated in view of the development of tolerance. In these patients a cross-tolerance to nitroglycerin was observed in that the usual tablet of nitroglycerin sublingually was less effective in abolishing the angina.

No methemoglobinemia was detected spectroscopically while giving the nitrates at any dosage level.

Since most of the patients taking part in this study were asymptomatic, more subjective complaints were recorded when they received the nitrates than the placebo. It should be emphasized, however, that this investigation was not designed for such a purpose. If it had been patients with symptoms would have been selected and the drugs administered so as to have avoided the development of complete or almost complete tolerance.

DISCUSSION

Since tolerance to mannitol and inositol hexanitrate develop and since they decrease systolic and diastolic blood pressure in adequate doses, no clinical investigation that we have been able to find has used them properly in hypertensive patients to test the assumption that the reduction in such patients is symptomatically, if not prophylactically beneficial.

Our results show, we believe, that these organic nitrates when used should be used as is indicated in current textbooks of pharmacology[1, 2]. Furthermore, our results show that unless the dose is individualized, as first suggested by Mathew,[7] these drugs are not being properly used. This applies both to the determination of the size and frequency of the initial dose which will lower blood pressure without producing undesirable side reactions and to the determination in each patient of the time required to develop tolerance to that dose and to lose the tolerance.

It would be important both from a clinical and pharmacological point of view to determine in each of a group of patients whether any symptomatic relief obtained during the period of the development of tolerance on the drug would carry over during a four- to five-day period while off the drug to lose the tolerance. This would be especially beneficial to that group of patients whose symptoms at first appear to be benefited.

We suspect that the continued rather extensive use by physicians of the organic nitrates

in view of the development of tolerance is not due to a placebo effect of some sort, but to the intermittent use of the drug by the patient. We have seen several patients who apparently had not developed a tolerance to the blood-pressure reducing effect of the drug; and on questioning them and counting the tablets taken it was found that they had not taken any tablets for several days, but had resumed their use before visiting us. As is well known, when symptoms disappear for a few days some patients are prone to discontinue their medicine and then take it again when the symptoms return or before revisiting their physician.

Conclusions

1. The literature reveals that in the use of mannitol hexanitrate and inositol hexanitrate and other nitrites and nitrates in the management of hypertension, the possibility of the development of tolerance to the blood pressure reducing effect of these drugs has been ignored.

2. The present study in which 32 patients were alternated between periods of nitrate and placebo medication shows that tolerance to the blood-pressure reducing effects of these drugs occurred in all. The tolerance is quite well established in most subjects in eight days and well established in 14 days when a blood-pressure reducing dose of mannitol or inositol hexanitrate is given four times a day. The tolerance to these slow and prolonged acting organic nitrates is apparently completely lost in 10 days. (It may be lost in less time, but we performed no definitive tests to determine the range in an adequate number of patients.)

3. The use of organic nitrites and nitrates in the management of hypertension should be carefully individualized by determining the optimal dose for the patient and the period of tolerance and of loss of tolerance [1, 2]. (Our study was not designed to compare the clinical effectiveness of the nitrates used with a placebo. To design adequately such a study, some knowledge regarding the development of tolerance to these drugs had to be obtained.)

4. In six hypertensive patients it was found that an oral dose of 0.12 Gm. of inositol hexanitrate on the average reduced the systolic pressure 44 mm. Hg and the diastolic 20 mm. Hg. The pressure had started to fall within 45 minutes, reached a maximum fall in from 60 to 150 minutes and had returned almost to the initial level in four and one half hours. Our observations on the blood-pressure reducing potency of mannitol hexanitrate as regards latent period of action, range of period of maximum fall and duration of fall confirm those in the literature[7, 35]. The effect of 0.25 Gm. of mannitol hexanitrate produced an effect approximately similar to that with 0.12 Gm. of inositol hexanitrate in our hypertensive patients.

Summario in Interlingua

Le presente studio clinic esseva interprendite proque le litteratura clinic in re le uso de hexanitratos de mannitol e inositol—e in grande mesura etiam del altere nitritos e nitratos empleate in le tractamento de hypertension—non se occupa del problema del disveloppamento e durantia del toleration. Nos ha constatate que toleration del action vasodilatatori de nitrato de mannitol e inositol se disveloppa intra 8 e 14 dies e se perde completemente intra 10 dies post abstiner le droga. Le uso de iste nitratos deberea esser cautemente individualisate per determinar le optime dosage e le tempore requirite pro le disveloppamento e le perdita del toleration.

REFERENCES

[1] Sollmann, T.: A manual of Pharmacology. Ed. 1, Philadelphia, W. B. Saunders, 1917.

[2] Goodman, L. and Gillman, A.: The Pharmacological Basis of Therapy. New York, MacMillan, 1941.

[3] Stewart, D. D.: Case report. Philadelphia Polyclinic. **6:** 43, 1888–9.

[4] Laws, G. D.: Effects of nitroglycerin on those who manufacture it. J.A.M.A. **31:** 793, 1898.

[5] Queries and minor notes: The administration of nitroglycerin. J.A.M.A. **44:** 486, 1905.

[6] Stewart, D. D.: Tolerance to nitroglycerine. J.A.M.A. **44:** 1678, 1905.

[7] Mathew, E.: Vasodilators in high blood pressure. Quart. J. Med. **2:** 261, 1908–09.

[8] Wallace, G. B. and Ringer, A. I.: The lowering of blood pressure by the nitrite group. J.A.M.A. **53:** 1629, 1909.

[9] White, P. D.: Heart Disease. Ed. 4, New York, MacMillan, 1951.

[10] Miller, J. L.: Hypertension and the value of the various methods for its reduction. J.A.M.A. **54:** 1666, 1910.

[11] Lawrence, C. H.: (a) The relation of hypertension to urinary excretion. Am. J. M. Sc. **144:** 330, 1912.
(b) —: The effect of pressure-lowering drugs and therapeutic measures on systolic and diastolic pressure in man. Arch. Int. Med. **9:** 409, 1912.

[12] Enright, G. E.: The effects of nitroglycerine on those engaged in its manufacture. J.A.M.A. **62:** 201, 1914.

[13] Heitz, J.: De l'état cardio-vasculaire des ouvrier fabriquant ou maniant habituellement la nitroglycerin. Arch. mal. coeur **17:** 578, 1924.

[14] Meyers, H. B. and Austin, V. T.: Nitrite toleration. J. Pharmacol. & Exper. Therap. **36:** 227, 1929.

[15] Crandall, L. A., Leake, D. C., Lovenhart, A. S. and Muehlberger, C. W.: Acquired tolerance to and cross-tolerance between the nitrous and nitric acid esters and sodium nitrite in man. J. Pharmacol. and Exper. Therap. **41:** 103, 1931.
(b) —: Pharmacology of nitrites. Ph.D. thesis, Northwestern University, 1928.

[16] Stroud, W. D.: The Diagnosis and Treatment of Cardiovascular Disease. Ed. 4, Philadelphia, F. A. Davis, 1950.

[17] Lewis, T.: Diseases of the Heart. London, MacMillan, 1946.

[18] Levy, R. L.: Disorders of the Heart and Circulation. New York, Thomas Nelson & Sons, 1951.

[19] Goldberger, E.: Heart Disease, Diagnosis and Treatment. Philadelphia, Lea and Febiger, 1951.

[20] Beckman, H.: Treatment in General Practice. Ed. 6, Philadelphia, W. B. Saunders Co., 1948.

[21] Meakins, J. C.: Practice of Medicine. St. Louis, C. V. Mosby Co., 1950.

[22] Cecil, R. L. and Loeb, R. F.: A Textbook of Medicine. Ed. 8. Philadelphia, W. B. Saunders Co., 1951.

[23] Chamberlin, E. N.: Textbook of Medicine. Baltimore, Williams & Wilkins, 1951.

[24] Harrison, T. R.: Principles of Internal Medicine. Philadelphia, Blakiston Co., 1950.

[25] Levine, S. A.: Clinical Heart Disease. Philadeldelphia, W. B. Saunders Company, 1945.

[26] Fishberg, A. M.: Hypertension and Nephritis. Ed. 5, Philadelphia, Lea and Febiger, 1954.

[27] Mason, E. C.: A note on water excretion as influenced by blood pressure response to sodium nitrite. J. Lab. & Clin. Med. **9:** 529, 1924.

[28] Burgess, A. M.: The reaction to nitrites in the anginal syndrome and arterial hypertension. Ann. Int. Med. **5:** 441, 1931.

[29] Weiss, S. and Ellis, L. B.: Influence of sodium nitrite on the cardiovascular system and on renal activity. Arch. Int. Med. **52:** 105, 1933.

[30] Leuth, H. C. and Hanks, T G.: Unusual reactions of patients with hypertension to glyceryl trinitrate. Arch. Int. Med. **62:** 92, 1938.

[31] Stieglitz, E. J.: Bismuth subnitrate in the treatment of arterial hypertension. J.A.M.A. **95:** 842, 1930.

[32] Ayman, D.: Bismuth subnitrate in the treatment of arteriolar hypertension. J.A.M.A. **98:** 545, 1932.

[33] Bruen, C.: The therapeutic efficacy of bismuth in arterial hypertension. Am. J. M. Sc. **188:** 21, 1934.

[34] Evans, W. and Loughinan, O.: The drug treatment of hyperpiesia. Brit. Heart J. **1:** 199, 1939.

[35] Weaver, J. C., J. H. Wills and Hodge, H. C.: The effect on the blood pressure of normal persons and the hypertensive patients of glyceryl trinitrate, sodium nitrite, erythrol tetranitrate, and mannitol hexanitrate. Am. Heart J. **28:** 601, 1941.

[36] Carrere-Comes, O., Squillace, A. and Rossi, R.: Sull'azione ipotensiva dei nitroderivati ed in particolare dell'esanitrato di mannitolo. Minerva med. **2:** 744, 1952.

[37] Boyer, N. H.: The treatment of hypertension. M. Clin. North America **26:** 1421, 1942.

[38] Zeiss, F. R. and W. A. Brams: Studies on the effect of nitroglycerin, amyl nitrite and acetylcholine on hypertension. Am. Heart J. **5:** 300, 1930.

[39] Wilkins, R. W., F. W. Haynes and Weiss, S.: The role of the venous system in circulatory collapse induced by sodium nitrite. J. Clin. Invest. **16:** 85, 1937.

[40] Wrightington, M.: Effect of organic nitrates on coronary flow. Proc. Soc. Exper. Biol. & Med. **52:** 184, 1943.

[41] Snedecor, G. W.: Statistical Methods, Ed. 4, Ames, Iowa, The Collegiate Press, 1946.

Newer Drugs in the Treatment of Hypertension

II. Use of Hexamethonium in Combination with Hydralazine

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Sixty-one patients exhibiting severe hypertensive vascular disease were treated with hexamethonium in combination with hydralazine for periods up to 22 months. Results, in terms of blood pressure control, were considerably better with combined therapy than with hexamethonium alone regardless of whether hydralazine was added to hexamethonium initially or later. Improvement in retinopathy and in the electrocardiogram was noted. The malignant phase of hypertensive disease was reversed in eight of nine instances. Late systemic reactions to hydralazine occurred in seven patients. One death, attributed to possible hexamethonium poisoning, was observed. Hexamethonium-hydralazine therapy represents a potent combination of drugs for the treatment of severe hypertensive vascular disease.

IN A PREVIOUS study it was demonstrated that hexamethonium, although a potent anticholinergic compound capable of lowering blood pressure for short periods, is not satisfactory as a single drug for the long-term treatment of severe hypertension.[1] While this study was in progress, preliminary clinical investigation of hydralazine (Apresoline) demonstrated this compound to be partially effective in the treatment of hypertension.[2-5] Hydralazine possesses complex actions which include the neutralization of pressor substances,[6-9] central vasodepression,[10, 11] weak adrenergic blocking effect,[12-16] and direct peripheral vasodilatation.[17] The discoveries that it increases renal blood flow[18] and decreases cerebral vascular resistance[19] concomitantly with fall in systemic blood pressure lent considerable interest to this agent. The rise in renal blood flow is associated with increased cardiac output and tachycardia;[20, 21] the latter effects can be prevented by prior administration of hexamethonium.[22] Subsequent clinical investigations[7, 23-28] have shown, with few exceptions,[29, 30] that hydralazine employed concurrently with hexamethonium is more effective in the treatment of hypertension than either agent used alone.

The present investigation was begun in an effort to study the effects of combined hexamethonium-hydralazine therapy in the long-term treatment of severe hypertension. Its purpose was two-fold: (1) to determine whether the combination of hexamethonium and hydralazine would be more effective than hexamethonium alone in controlling hypertensive disease (a) when hydralazine was added after months of hexamethonium administration, or (b) when administration of the two agents was begun concomitantly; and (2) to evaluate critically the usefulness of combined hexa-

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Adequate supplies of hexamethonium compounds were provided by Ciba Pharmaceutical Products, Inc., Summit, New Jersey; and Chilcott Laboratories Division of the Maltine Company, Morris Plains, New Jersey (now Warner-Chilcott Laboratories, New York, N. Y.). Hydralazine hydrochloride (Apresoline) was generously supplied by Ciba Pharnaceutical Products, Inc., Summit, N. J.

methonium-hydralazine therapy in the long-term management of the patient exhibiting severe hypertension.

Material and Methods

Sixty-one patients with severe, stable or progressive hypertensive vascular disease with an average systolic and diastolic blood pressure of 212/130 were selected for study. Thirty-one of these patients, comprising series I, were individuals already under treatment with hexamethonium alone, and had been treated for periods of 3 to 27 months (average 10 months) before hydralazine was added. Hydralazine was added to hexamethonium in these 31 patients for one of the following reasons: (1) unsatisfactory response to hexamethonium alone in spite of adequate trial; (2) failure to maintain initial good response with continued administration of the drug. Series II consisted of 30 patients who were treated concurrently with hexamethonium and hydralazine from the outset.

In series I, the ages of the 31 patients ranged between 31 and 65 years with an average age of 50 years. There were 24 males and 7 females. According to Palmer's classification of hypertension[31] they may be grouped before treatment was instituted as follows: grade II, 15 patients; grade III, 15 patients; grade IV, one patient. One or more serious complications of hypertension had occurred in 13 patients prior to treatment: cerebrovascular accidents in 6; myocardial infarction in 4, angina pectoris in 2; and paroxysmal nocturnal dyspnea in 2. In series II, the ages of the 30 patients ranged between 15 and 57 years with an average of 44 years. There were 16 males and 14 females. According to Palmer's classification the group may be divided as follows: grade II, 11 patients; grade III, 11 patients; grade IV, 8 patients. One or more serious complication of hypertension had occurred in 15 patients: cerebrovascular accidents in five; encephalopathy in four; angina pectoris in one; and previous congestive heart failure in five. Two patients, one in each series, had undergone lumbar sympathectomy (Smithwick) with subsequent return of hypertension.

Fifty-one of the 61 patients, 25 in series I and 26 in series II, were hospitalized for periods varying from one to six weeks for institution of therapy. Six patients in series I and 4 in series II were treated entirely on an out-patient basis. Prior to treatment each patient was thoroughly studied by conventional methods previously described.[1]

In all patients in both series hexamethonium therapy was instituted before hydralazine was added. Hexamethonium was administered in accordance with the principles and precautions outlined elsewhere.[1] Fifty-five of the patients were given hexamethonium in oral form; parenteral therapy was reserved principally for patients demonstrating malignant hypertension, significant evidence of arterial disease, or impairment of renal function. Six patients were begun on parenteral hexamethonium chloride while in the hospital, and five were transferred to the oral form before discharge. All 31 patients in series I were receiving maximum tolerated doses of hexamethonium when hydralazine was instituted. Seven patients were rehospitalized for the addition of hydralazine; in 24 patients hydralazine was added cautiously on an out-patient basis. For the 30 patients in series II, hydralazine was added to hexamethonium when significant postural fall in the blood pressure was observed. This was usually accomplished within a week after institution of hexamethonium therapy in the hospital and within several weeks in the out-patient clinic.

The initial dose of hydralazine was 10 mg. to 25 mg. four times a day, administered with the hexamethonium on an empty stomach. Increments of 10 mg. to 25 mg. per dose were made as rapidly as tolerance permitted until the blood pressure had stabilized at a satisfactory level. During combined therapy dosage of hexamethonium ranged from 0.75 Gm. to 4.75 Gm. per day with an average dosage of 1.8 Gm. per day. Dosage of hydralazine ranged from 75 mg. to 1100 mg. per day with an average dosage of 418 mg. per day. All patients with malignant hypertension were treated initially with the rice diet in addition to drugs. As improvement occurred, gradual dietary modification was made to standard low sodium diets. Low sodium diets generally were instituted initially for most patients; liberalization of diet was allowed after control of blood pressure was achieved.

During hospitalization recumbent and standing blood pressures were recorded four times daily, and, following discharge, at approximately weekly intervals. Every six months cardiac and renal status were re-evaluated by means of urinalysis, blood nonprotein nitrogen, phenolsulphonphthalein excretion test, electrocardiogram and teleroentgenogram. The blood pressure response for each patient was averaged monthly and subdivided into three treatment periods (hospitalization, first four months of out-patient care, and five months plus of out-patient follow-up) in order to detect any tendency for blood pressure control to be lost or to escape during continued therapy. Although both standing and recumbent pressures were recorded and subjected to analysis, only recumbent blood pressure was used for interpretation of results.

In assessing the efficacy of therapy in controlling blood pressure, two methods of approach were used. First, for each treatment period the patients were separated into three arbitrary, previously defined groups,[1] group A, "good," group B, "fair," group C, "poor," according to recumbent blood pressure

response.* Second, fall in mean recumbent blood pressure during each period was determined. Mean pressure was calculated by adding one-third of the pulse pressure to the diastolic pressure. A fall of 20 mm. Hg or greater was considered a definite response.

Retinopathy was graded according to the Keith-Wagener classification. Heart size was determined for each patient from serial teleoroentgenograms; percentage deviation from average normal heart size was calculated from the Ungerleider table.[32] Patients exhibiting a deviation from normal of more than plus 10 per cent were regarded as having cardiac enlargement. During therapy an increase or decrease in percentage deviation of more than 10 per cent was considered a significant change. Renal function was evaluated by conventional excretory and concentration tests.

Results

All 61 patients experienced symptoms from hexamethonium which tended to diminish but did not disappear entirely during treatment. The most common of these recurrent troublesome reactions were dryness of the mouth, episodes of faintness, constipation, blurred vision, feelings of weakness and fatigue, and impotence. At the time when hydralazine was added to hexamethonium, approximately one-fourth of all the patients experienced a transient increase in the number of episodes of weakness and faintness. Later there was amelioration of the postural symptoms from hexamethonium in some patients in series I, due to decrease in dosage of hexamethonium (from an average dose of 2.4 mg. per day before hydralazine to 1.8 mg. per day after hydralazine).

Forty-five of the 61 patients, 22 in series I and 23 in series II, initially experienced one or more hydralazine effects. The most frequently encountered reactions were headache, palpitation, nausea, nasal congestion, and mild edema. These symptoms generally were much less severe and troublesome than those resulting from hexamethonium and, with few exceptions, tended to disappear or diminish greatly during continued administration of the drug. Gradual titration of hydralazine dosage unquestionably decreased unpleasant side reactions to the drug. Four of the 61 patients, one in series I and three in series II, discontinued both drugs after less than five months, primarily because of distressing symptoms from hexamethonium. One patient discontinued hydralazine upon the advice of his personal physician. Three additional patients in series I took both drugs irregularly, and in them follow-up was inadequate.

Table 1.—*Complications Observed During Therapy*

	Series I, Hexamethonium, 31 Patients	Series I, Hexamethonium-Hydralazine, 31 Patients	Series II, Hexamethonium-Hydralazine, 30 Patients
Deaths		4*	3
Combined cardiac and renal failure		1	
Cerebral vascular accident and uremia		1	
Congestive heart failure		1	
Probable myocardial infarction		1	
Subarachnoid hemorrhage			1
Cerebral hemorrhage			1
Uremia and ? hexamethonium poisoning			1
Nonfatal complications	4	4	2
Coronary insufficiency	1	1	2
Myocardial infarction	1	1	
Congestive heart failure	1	1	
Cerebral thrombosis	1	1	
Late systemic reactions to hydralazine		1	6

* Numerals refer to number of patients.

Complications

Table 1 presents the complications encountered during therapy.

Seven deaths occurred among the 61 patients, four in series I after the addition of hydralazine and three in series II. These include fatalities

* Group A includes those patients whose average blood pressure fell to 160/110 or less; group B comprises those patients whose average blood pressure fell to 180/115 or less; and group C contains those patients whose average blood pressure response failed to reach the latter level.

TABLE 2.—*Effect of Hexamethonium with Late and with Initial Hydralazine upon Recumbent Blood Pressure*

	Series I—31 Patients					Series II—30 Patients		
	Hexamethonium			Hexamethonium-hydralazine		Hexamethonium-hydralazine		
	Hospital	First 4 months	5–26 months	First 4 months	5–22 months	Hospital	First 4 months	5–17 months
Group A.....	9*	3	1	5	10	10	9	10
Group B.....	5	6	6	13	8	10	9	8
Group C.....	11	21	23	8	8	6	8	6
Totals.....	25	30	30	26	26	26	26	24

* Numerals refer to number of patients.

TABLE 3.—*Effect of Hexamethonium with Late and with Initial Addition of Hydralazine upon Mean Recumbent Blood Pressure*

Fall in Mean Recumbent Pressure, mm. Hg	Series I					Series II		
	Hexamethonium			Hexamethonium-hydralazine		Hexamethonium-hydralazine		
	Hospital	First 4 months	5–26 months	First 4 months	5–22 months	Hospital	First 4 months	5–17 months
0–9	3*	11	7	3	1	2	2	2
10–19	5	3	13	6	5	4	5	4
20–29	7	9	3	5	2	6	9	5
30–39	7	5	3	4	10	8	2	7
40–49	2	1	3	5	1	5	5	1
50–59	1	1	1	3	5	1	3	3
60+	0	0	0	0	2	0	0	2
Totals.....	25	30	30	26	26	26	26	24

* Numerals refer to number of patients.

from cardiac causes, cerebral vascular accidents, and renal insufficiency. In one patient exhibiting malignant hypertension and death in uremia, acute hexamethonium poisoning was suspected. Four nonfatal complications had occurred among the 31 patients in series I before hydralazine was added. Among all 61 patients in both series, six nonfatal complications occurred during combined hexamethonium-hydralazine therapy, four in series I and two in series II. Initial episodes of coronary insufficiency in two patients were attributed to hydralazine; the other complications were ascribed to the severity of the hypertensive disease itself.

Seven of the 61 patients, one in series I and six in series II, developed late systemic reactions to hydralazine which necessitated discontinuance of the drug in each instance. Six of these reactions were characterized by symptoms and signs suggestive of rheumatoid arthritis; and one patient exhibited, in addition, pleuritis with effusion, pericarditis with effusion, fever, and "L.E." cells in the peripheral blood. The features of these reactions are presented in detail elsewhere.[33]

Effect Upon Blood Pressure

Table 2 presents the blood pressure responses of all 61 patients treated with hexamethonium and hydralazine in combination, according to the arbitrarily defined groups A, B, C. Fifty of the 61 patients continued combined therapy for five months or longer and were satisfactorily followed. Thirty of the 31 patients in series I had been treated with hexamethonium alone for five months or longer before hydralazine was added. The failure of hexamethonium alone to maintain good control of blood pressure, except for one of 30 patients, throughout prolonged therapy is apparent in table 2. This loss of blood pressure control occurred despite increases in dosage of hexamethonium to maximum tolerated levels in each patient. The addition of hydralazine to these same patients in series I, however, resulted in far better control of blood pressure during prolonged observation. Ten of 26 patients were well controlled. In series II, an approximately equal proportion of patients demonstrated "good" control of blood pressure during each treatment period. There was no tendency for control of pressure to be lost during prolonged therapy. Ten of 24 patients remained well controlled. The better results in series II during initial periods of treatment are attributed to earlier titration of more effective combined drug dosage. After five months of combined therapy no significant differences are noted between results in series I and series II.

Table 3 presents an analysis of the fall in the mean recumbent blood pressure during

each treatment period as compared with pretreatment averages. In series I the tendency for the blood pressure to rise during prolonged therapy with hexamethonium alone is again evident so that in the late follow-up period only 10 of 30 (33 per cent) patients demonstrated a fall in mean pressure of 20 mm. Hg or greater. After the addition of hydralazine to these same patients, however, a fall in mean pressure of this magnitude was observed in 17 of 26 during the first four months of outpatient care and in 20 of 26 (77 per cent) patients during the late follow-up period. In series II approximately three-fourths of the patients exhibited a fall in mean pressure of 20 mm. Hg or greater throughout each treatment period.

The majority of patients in both series I and series II who had a "good" (group A) or "fair" (group B) blood pressure response to combined therapy in the late treatment period exhibited a fall in mean recumbent blood pressure of 20 mm. Hg or greater. Nine of 14 group C patients in both series exhibited a fall in mean recumbent pressure of this magnitude, yet demonstrated relatively "poor" blood pressure control.

Effect Upon Retinopathy

In series I during treatment with hexamethonium alone no progression of retinopathy was observed and the fundi of six patients improved as follows: five from grade III to grade II and one from grade IV to grade III. After the addition of hydralazine to these patients, two patients with grade III fundi improved to grade II, and the retinopathy of two patients, with "poorly" controlled blood pressure, worsened from grade II to grade III. In series II retinopathy did not progress in any patient during combined therapy, and the fundi of 11 patients improved as follows: three from grade IV to grade II, five from grade IV to grade III, and three from grade III to grade II.

Effect Upon Heart Size

Prior to therapy 23 patients (8 in series I and 15 in series II) had enlarged hearts; the remaining 38 patients had normal-sized hearts.

In series I during treatment with hexamethonium alone one patient with "good" control of blood pressure demonstrated a significant decrease in heart size, and two patients with "poorly" controlled blood pressure exhibited a definite increase in heart size. In series I after the addition of hydralazine and during combined therapy no patient demonstrated a significant increase or decrease in heart size. In series II during combined hexamethonium-hydralazine therapy two patients, both of whom initially were in congestive heart failure and subsequently had "poor" control of blood pressure, showed a significant decrease in heart size, while one patient with "poor" blood pressure control exhibited a significant increase in heart size.

TABLE 4.—*Effect of Hexamethonium alone and in Combination with Hydralazine upon Fundi, Heart Size, Electrocardiogram and Renal Function*

	Series I				Series II	
	Hexamethonium, 31 patients		Hexamethonium-hydralazine, 31 patients		Hexamethonium-hydralazine, 30 patients	
	Improved	Worse	Improved	Worse	Improved	Worse
Fundi	6*	0	2	2	11	0
Heart size	1	2	0	0	2	1
ECG	4	1	4	1	8	0
Renal funct.	0	1	0	2	0	1

* Numerals refer to number of patients.

Effect Upon Electrocardiogram

Thirty-six patients, 18 in each series, demonstrated ST-T changes of "left ventricular strain pattern" prior to therapy. In series I during treatment with hexamethonium alone, four patients showed improvement in the "strain pattern", and in three of these the ST-T changes reverted entirely to normal. After addition of hydralazine to this group and during combined therapy, four patients demonstrated improvement in the ST-T pattern, with reversion to normal in two instances, while one patient demonstrated an increase in the "strain pattern". In series II during combined therapy 8 of 18 abnormal electrocardiograms improved, and in six of these there was a complete reversal of the ST-T "strain pattern" to normal.

Effect Upon Renal Function

Before treatment 36 patients (15 in series I and 21 in series II) showed proteinuria, and eight patients (three in series I and five in series II) exhibited impaired renal function as measured by the standard laboratory tests. In series I, during therapy with hexamethonium alone, one patient developed impairment of renal function which subsequently progressed and two patients developed slight proteinuria. In both series, during combined hexamethonium-hydralazine therapy, three patients with impaired renal function (two in series I and one in series II) exhibited progressive impairment of function terminating in renal insufficiency and death in uremia. During combined therapy one patient in series I developed slight proteinuria.

Discussion

Hexamethonium and hydralazine administered simultaneously constitute a potent combination of hypotensive drugs, capable of achieving and maintaining for prolonged periods significant reduction of blood pressure in the majority of patients exhibiting severe hypertensive vascular disease. Previous extended experiences with hexamethonium administered alone indicated this compound to have limited utility in severe hypertensive disease because of the gradual loss of blood pressure control after months of continued therapy. The addition of hydralazine to a group of patients responding poorly to long-term hexamethonium treatment resulted in further reduction of mean blood pressure and more satisfactory control of blood pressure for most individuals. In these patients it permitted reduction in average daily dosage of hexamethonium; slight amelioration of the side-effects from hexamethonium followed. No appreciable difference was noted in the final results between the late and early addition of hydralazine to hexamethonium therapy, although in the latter instance initial effects upon blood pressure were better due to earlier titration of hydralazine dosage. During combined therapy no tendency for blood pressure control to "escape" was evident after months of uninterrupted therapy.

Especially gratifying were the responses of nine patients suffering from malignant hypertension, four of whom had impaired renal function and three of whom had nitrogen retention. The rice diet, later modified to standard low sodium diet, was used initially in all nine patients. Eight patients exhibited reversal of the malignant phase, one while receiving hexamethonium alone, and seven during combined treatment, initially instituted. Two of the nine patients subsequently died; one patient responded poorly to therapy and died of uremia and possible hexamethonium poisoning; the other succumbed to subarachnoid hemorrhage from cerebral aneurysm several months after discontinuing both drugs. It has been our experience that the young malignant hypertensive patient who possesses good renal function is particularly sensitive and responsive to combined drug and dietary therapy. Our observations generally are in accord with those reported by Schroeder.[27, 34]

Dietary restriction of sodium has been demonstrated to potentiate the hypotensive effect of hexamethonium,[26] and hydralazine[2, 35] used separately. Sodium restriction may have played some part in decreasing blood pressure in many of our patients. Its exact contribution is difficult to assess in a clinical study of this type.

During combined hexamethonium-hydralazine therapy, approximately one-fifth (20 per cent) of all patients exhibited improvement in retinopathy and in the electrocardiogram. It is to be noted that improvement in retinopathy and in the electrocardiogram had already occurred in a significant number of patients in series I during treatment with hexamethonium alone; hence the addition of hydralazine produced relatively little further change in these areas. Little effect was noted either upon heart size or renal function during combined therapy.

Although in most patients partial relief was obtained from the unpleasant reactions to hexamethonium during prolonged treatment, in many patients these effects continued to constitute a major problem, actually causing four patients to discontinue the drugs altogether and three others to take medication sporadically. Severe postural hypotension was

a potential hazard throughout treatment. Symptoms from hydralazine were less severe and troublesome and tended to disappear in nearly all patients. Two patients without previous evidence of coronary disease experienced attacks of chest pain associated with minor electrocardiographic changes and were considered to have mild acute coronary insufficiency. No patient with preexisting angina experienced an increase in frequency or severity of pain during treatment with hydralazine. No instance of gastrointestinal bleeding was observed.

That combined hexamethonium-hydralazine therapy may not prevent serious or fatal vascular complications of hypertension is evidenced by the incidence of deaths (seven patients or 11 per cent), and nonfatal complications (six patients or 9.8 per cent) observed during the study. The late systemic reactions to hydralazine observed in seven (11 per cent) patients[33] were a serious and unexpected development, necessitating withdrawal of the drug in each of these patients, and corticotropin and cortisone therapy in one before recovery ensued. The troublesome reactions from hexamethonium, including postural hypotension, and the potential complications from hydralazine do not seem to warrant the use of combined hexamethonium-hydralazine in the long-term treatment of patients with mild essential hypertension.

Summary

(1) Sixty-one patients with severe hypertensive vascular disease, including nine patients with malignant hypertension, were treated with combined hexamethonium-hydralazine over periods of from 5 to 22 months for an average of 10 months per patient.

(2) In the majority (76 per cent) of these patients definite reduction in recumbent blood pressure (fall in mean recumbent blood pressure of 20 mm. Hg or greater) was achieved and maintained throughout therapy, and approximately 40 per cent of the patients treated in the late follow-up period demonstrated "good" control of recumbent blood pressure (average recumbent pressure 160/110 or lower). No tendency for initial blood pressure reduction or control to be lost was observed.

(3) When hydralazine was added to 31 patients who had been under treatment with hexamethonium alone for periods of 5 to 26 months (average 10 months), further reduction in mean blood pressure and more satisfactory control of recumbent blood pressure were achieved in the majority of instances.

(4) The late addition of hydralazine to hexamethonium produced equally good eventual blood pressure reduction and control as did the initial combination of the two drugs; in the latter instance, however, better results during combined therapy were achieved earlier.

(5) Improvement in retinopathy and in the electrocardiogram occurred in one-fifth of all patients during combined therapy, while little appreciable effect upon renal function or heart size was noted.

(6) Vascular complications incident to the hypertensive process were not prevented by therapy. Seven deaths (11 per cent) occurred, only one of which was attributed to the drugs. Six nonfatal complications also appeared during treatment.

(7) Late systemic reactions to hydralazine were observed in seven (11 per cent) patients; in one patient the illness simulated disseminated lupus erythematosus and necessitated corticotropin and cortisone therapy.

(8) Combined hexamethonium-hydralazine therapy together with rigid dietary restriction of sodium constitutes at present an effective form of treatment for malignant hypertension and severe essential hypertension when renal function is good. The hazard of late systemic reactions to hydralazine limits the usefulness of this drug in the long-term therapy of hypertension.

Summario in Interlingua

Sexanta-un patientes con sever morbo vascular hypertensive esseva tractate con hexamethonium in combinationes con hydralazina pro periodos usque a 22 menses. Le resultatos obtenite in le controlo del pression sanguinee esseva considerabilemente melior con le therapia combinate que con hexamethonium sol, sin reguardo a si le hydralazina esseva addite

al hexamethonium initialmente o plus tarde. Esseva notate un melioration del retinopathia e del configurationes electrocardiographic. In 8 ex 9 casos le maligne phase del morbo hypertensive esseva revertite. Tardive reactiones systemic a hydralazina esseva notate in 7 patients. Un morte esseva possibilemente attribuibile a toxicosis hexamethonial. Therapia combinate de hexamethonium e hydralazina insimul con rigide restrictiones dietari de natrium representa hodie un efficace forma de tractamento pro maligne hypertension e sever hypertension essential si le functionamento renal es bon. Le risco de retardate reactiones systemic a hydralazina limita le utilitate de iste droga in le therapia hypertensive a longe durantia.

REFERENCES

[1] Sieber, H. A., Grimson, K. S. and Orgain, E. S.: Newer drugs in the treatment of hypertension. I. Use of hexamethonium salts. Circulation **8:** 840, 1953.

[2] Schroeder, H. A.: The effect of 1-hydrazinophthalazine in hypertension. Circulation **5:** 28, 1952.

[3] Johnson, R. L., Freis, E. D. and Schnaper H. W.: Clinical evaluation of *l*-hydrazinoph-, thalazine (C-5968) in hypertension with special reference to alternating treatment with hexamethonium. Circulation **5:** 833, 1952.

[4] Taylor, R. D., Dustan, H. P., Corcoran, A. C. and Page, I. H.: Evaluation of 1-hydrazinophthalazine ("Apresoline") in treatment of hypertensive disease. Arch. Int. Med. **90:** 734, 1952.

[5] Hafkenschiel, J. H. and Lindauer, M. A.: *l*-Hydrazinophthalazine (Apresoline) in the treatment of hypertension: A two year study. Circulation **7:** 52, 1953.

[6] Taylor, R. D., Page, I. H. and Corcoran, A. C.: A hormonal neurogenic vasopressor mechanism. Arch. Int. Med. **88:** 1, 1951.

[7] Schroeder, H. A.: Control of hypertension by hexamethonium and 1-hydrazinophthalazine: Preliminary observations. Arch. Int. Med. **89:** 523, 1952.

[8] Helmer, O. M. Cited by Schroeder.[7]

[9] Freis, E. D. and Finnerty, F. A., Jr.: Suppression of vasomotor reflexes in man following 1-hydrazinophthalazine (C-5968). Proc. Soc. Exper. Biol. & Med. **75:** 23, 1950.

[10] Gross, F., Druey, J. and Meier, R.: A new group of depressor substances with a special type of effect. Experientia **6:** 19, 1950.

[11] Craver, B. N., Barrett, W., Cameron, A. and Yonkman, F. F.: Activities of 1-hydrazinophthalazine (Ba-5968): Hypotensive agent. J. Am. Pharm. A. (Scient. Ed.) **40:** 559, 1951.

[12] Grimson, K. S., Chittum, J. R. and Metcalf, B. H.: Actions of *l*-hydrazinophthalazine (C-5968) on vasomotor reflexes and hypertension in dogs and man. Federation Proc. **9:** 279, 1950.

[13] Walker, H. A., Wilson, S. and Richardson, A. P.: Effect of 1-hydrazinophthalazine (C-5968) on cardiovascular system of unanesthetized dogs. Federation Proc. **9:** 323, 1950.

[14] Gross, F., Schuler, W., Tripod, J. and Meier, R.: Hemmung der Diaminooxydase (Histaminase) durch Phthalazinderivate. Experientia **8:** 229, 1952.

[15] Schroeder, H. A.: Effects on hypertension of sulfhydryl and hydrazine compounds. J. Clin. Invest. **30:** 672, 1951.

[16] Walker, H. A., Wilson, S., Atkins, E. C., Garret, H. E. and Richardson, A. P.: The effect of *l*-hydrazinophthalazine (C-5968) and related compounds on the cardiovascular sytem of dogs. J. Pharmacol. & Exper. Therap. **101:** 368, 1951.

[17] Stunkard, A., Wertheimer, L. and Redisch, W.: Studies on hydralazine: Evidence for a peripheral site of action. J. Clin. Invest. **33:** 1047, 1954.

[18] Reubi, F. C.: Renal hyperemia induced in man by a new phthalazine derivative. Proc. Soc. Exper. Biol. & Med. **73:** 102, 1950.

[19] Hafkenschiel, J. H., Friedland, C. K., Yobaggy, J. and Crumpton, C. W.: Effects of 1-hydrazinophthalazine on cerebral hemodynamics and oxygen metabolism in hypertensive subjects. J. Pharmacol. & Exper. Therap. **103:** 345, 1951.

[20] Moyer, J. H., Handley, C. A. and Huggins, R. A.: Some pharmacodynamic effects of 1-hydrazinophthalazine (C-5968) with particular reference to renal function and cardiovascular response. J. Pharmacol. & Exper. Therap. **103:** 368, 1951.

[21] Wilkinson, E. L., Backman, H. and Hecht, H. H.: Cardiovascular and renal adjustments to a new hypotensive agent (Ciba-5968). Am. J. Med. **13:** 101, 1952.

[22] Moyer, J. H., Huggins, R. A. and Handley, C. A.: Further cardiovascular and renal hemodynamic studies following the administration of hydralazine (*l*-hydrazinophthalazine) and the effect of ganglionic blockade with hexamethonium on these responses. J. Pharmacol. & Exper. Therap. **109:** 175, 1953.

[23] Freis, E. D.: Methonium compounds in hypertension. Letter to the Editor. Lancet **1:** 909, 1951.

[24] Moyer, J. H.: Hydralazine (Apresoline) hydro-

chloride. Pharmacological observations and clinical results in the therapy of hypertension. Arch. Int. Med. **91:** 419, 1953.

[25] MOYER, J. H., SNYDER, H. B., JOHNSON, I., MILLS, L. C. AND MILLER, S. I.: Results with oral hexamethonium alone and in combination with 1-hydrazinophthalazine (Apresoline) in the therapy of hypertension. Am. J. M. Sc. **225:** 379, 1953.

[26] GROB, D. AND LANGFORD, H. G.: Further observations on the effects of autonomic blocking agents in patients with hypertension. I. General systemic effects of hexamethonium, pentamethonium, and hydrazinophthalazine. Circulation **8:** 205, 1953.

[27] SCHROEDER, H. A., MORROW, J. D. AND PERRY, H. M., JR.: Studies on the control of hypertension by Hyphex. I. Effects on blood pressure. Circulation **8:** 672, 1953.

[28] FREIS, E. D., FINNERTY, F. A., JR., SCHNAPER, H. W. AND JOHNSON, R. L.: The treatment of hypertension with hexamethonium. Circulation **5:** 20, 1952.

[29] HILKER, R. R. J., RHOADS, P. S. AND BILLINGS, C. E.: Clinical use of hydralazine and hexamethonium in treatment of hypertension. J. A. M. A. **153:** 5, 1953.

[30] KHAN, M. A.: Effect of hydralazine in hypertension. Brit. M. J. **1:** 27, 1953.

[31] PALMER, R. S., LOOFBOUROW, D. AND DOERING, C. R.: Prognosis in essential hypertension: Eight-year follow-up study of 430 patients on conventional medical treatment. New England J. Med. **239:** 990, 1948.

[32] UNGERLEIDER, H. E. AND GUBNER, R.: Evaluation of heart size measurements. Am. Heart J. **24:** 494, 1942.

[33] MULLER, J. C., RAST, C. L., JR., PYROR, W. W. AND ORGAIN, E. S.: Late systemic complications of hydralazine (Apresoline) therapy. J. A. M. A. **157:** 894, 1955.

[34] SCHROEDER, H. A., MORROW, J. D. AND PERRY, H. M., JR.: Studies on the control of hypertension by Hyphex. V. Effects on the course of the malignant stage. Circulation **10:** 321, 1954.

[35] GILL, R. J., DUNCAN, G. G. AND REINHARDT, D. J.: Arterial hypertension: The therapeutic effect of sodium restriction combined with 1-hydrazinophthalazine or dibenzyline. Am. J. M. Sc. **226:** 249, 1953.

The Role of Pulmonary Hypertension and Thromboembolism in the Production of Pulmonary Arteriosclerosis

By ROBERT M. O'NEAL, M.D. AND WILBUR A. THOMAS, M.D.

Thromboembolism and pulmonary hypertension have been assessed as factors in the production of pulmonary arteriosclerosis. A study was made of autopsy records and tissue sections from 59 cases of congenital heart disease with anomalies permitting shunting of blood from the systemic to the pulmonary circulation and 31 cases of pulmonary stenosis with septal defect. Pulmonary arteriosclerosis was found to be common and of equal frequency in the two groups of cases, indicating that hypertension is not a necessary factor. There was a close correlation between the presence of pulmonary arterial thrombi and pulmonary arteriosclerosis.

EXTENSIVE STUDIES of pulmonary arteriosclerosis have disclosed a number of etiologic factors of possible importance. Hypertension and thromboembolism are the two factors that have been recently considered most important. Another factor which must be considered in certain cases is increased rate of flow.

Thrombo-embolism: The work of Duguid[1] has stimulated a series of experiments demonstrating that fibrous intimal plaques can be produced in the pulmonary arteries of rabbits by intravenous injection of emboli composed of blood clot.[2-6] It has been established by Rich[7] that pulmonary arterial thrombi frequently occur in patients with congenital pulmonary stenosis. He attributed this frequency to sluggish pulmonary blood flow and polycythemia, both of which increase the likelihood of intravascular thrombosis. In the study being presented here, a search for thrombi in the pulmonary arteries has also been made on a series of cases of the hemodynamically opposite conditions, the congenital anomalies with shunting of blood from the systemic circulation to the pulmonary circulation (hereinafter referred to as left-to-right shunt). These patients with left-to-right shunt usually have normal or reduced numbers of circulating erythrocytes.[8] They also have increased rate of pulmonary blood flow or pulmonary hypertension, or both. Several reports have described thrombosis of small pulmonary arteries in such cases, but these cases have commonly been classified as "pulmonary arteritis".[9, 10]

Hypertension: The fibrous intimal thickening often described in cases with left-to-right shunt has been considered the result of pulmonary hypertension.[11] Barnard[6] considered the concentric fibrous intimal lesions found in the pulmonary arteries of rabbits injected intravenously with blood clot to be due to concomitant hypertension.

In this study we are evaluating the effect of pulmonary hypertension on the pulmonary arteries in cases of congenital heart disease with left-to-right shunt. Comparison will be made with cases having pulmonary valvular or infundibular stenosis and a septal defect (hereinafter referred to as "pulmonary stenosis"), mainly tetralogy of Fallot, which in general have low or normal pulmonary arterial pressures,[12] and with "normal" controls.

Rate of Flow: Patients with congenital anomalies that permit left-to-right shunting of blood must have either increased rate of pulmonary blood flow, pulmonary hypertension, or both. Exact physiologic data are necessary to determine the rate of flow but they are not available in these cases, making it impossible to evaluate rate of flow *per se* as a factor. Nevertheless, increased rate of flow has been considered as a factor in the genesis of arteriosclerosis in other

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TABLE 1—*Differences Between the Two Abnormal Groups of Congenital Cardiovascular Anomalies Contributing to Their Usefulness in This Study*

	Polycythemia	Pulmonary hypertension and/or increased rate of flow	Pulmonary arterial thrombi	Pulmonary arteriosclerotic lesions
Pulmonary stenosis	Common	Low	Common	?
Left-to-right shunts	Uncommon	High	?	Common

TABLE 2—*Congenital Cardiac Anomalies with Left-to-Right Shunt*

Case No.	Age	Type of defects and diameters*	Microscopic thrombi in pul. arteries†	Fibrous intimal thickening in pul. arteries & arterioles†		Medial hypertrophy†
				Severity	Frequency	
1	3 mos.	I.A. 2 by 1 cm.; I.V. 0.6 by 0.4 cm.	0	0	0	3
2	3 mos.	I.V. 0.7 cm. with over-riding aorta; D.A. 0.1 cm.	0	0	0	3
3	3 mos.	I.V. 1.1 cm.	0	0	0	3
4	3 mos.	D.A. 0.6 cm.; subaortic stenosis	0	0	0	3
5	3 mos.	I.V. 0.4 cm.; I.A. 1.0 cm.	0	0	0	2
6	3 mos.	I.V. 0.2 cm.; D.A.; Trans.	0	1	1	0
7	3½ mos.	I.V. 0.5 cm. with over-riding aorta	0	0	0	3
8	4 mos.	D.A. "widely patent"	0	0	0	0
9	4 mos.	I.V. 0.6 cm.	0	0	0	1
10	4 mos.	I.V. 0.8 cm.; I.A.; D.A.	0	0	0	3
11	4 mos.	I.V. septum absent	0	0	0	3
12	4 mos.	I.V. 1 by 0.5 cm.	0	0	0	3
13	4½ mos.	I.V. "large" with over-riding aorta and aplasia of mitral valve	0	0	0	3
14	4½ mos.	I.V.	0	0	0	3
15	5 mos.	I.A. 1.3 by 1.5 cm.; I.V. 1.0 cm.	0	0	0	0
16	5 mos.	I.V. with overriding aorta	0	0	0	3
17	5 mos.	Aorta arising from pul. artery	0	0	0	1
18	6 mos.	I.V. with overriding aorta	0	2	1	0
19	6 mos.	"Large" septum primum defect	0	0	0	0
20	6 mos.	I.V. 0.5 cm.	0	0	0	0
21	7 mos.	I.V. 0.7 cm. with overriding aorta	0	0	0	0
22	7 mos.	I.V.; D.A.; coarctation	0	2	1	1
23	7 mos.	"Large" I.A.; Trans.	0	1	2	0
24	8 mos.	I.V. 1 by 0.4 cm. with coarctation	0	1	1	3
25	8½ mos.	I.V. 1.0 cm.	0	2	1	0
26	9 mos.	I.V. 1.2 cm. with overriding aorta	0	0	0	2
27	9 mos.	I.V. 0.6 cm.; Trans.	3	3	2	0
28	11 mos.	I.V. 1.0 cm.; persistent truncus	0	0	0	2
29	12 mos.	I.V. septum absent	0	0	0	3
30	12 mos.	I.V. and I.A. septa absent	0	0	0	0
31	13 mos.	I.A. "large"	1	3	2	2
32	15 mos.	I.V. with overriding aorta; D.A.; I.A.	0	0	0	3
33	16 mos.	I.V. with overriding aorta	0	0	0	3
34	16 mos.	I.V. with overriding aorta	0	0	0	0
35‡	16 mos.	I.V. septum absent; I.A.; agenesis mitral valve	2	3	2	2
36	17 mos.	I.V. 2 by 1 cm.; I.A. 2.2 by 0.5 cm.	0	0	0	3
37	18 mos.	D.A. 0.8 cm.	0	0	0	3
38	21 mos.	I.V. "large"	0	3	1	3
39	2⅓ yrs.	I.V.	0	1	1	3
40‡	2½ yrs.	I.V. 2.0 cm.; Trans.	3	3	3	0

TABLE 2—*Continued*

Case No.	Age	Type of defects and diameters*	Microscopic thrombi in pul. arteries†	Fibrous intimal thickening in pul. arteries & arterioles†		Medial hypertrophy†
				Severity	Frequency	
41	3 yrs.	I.V. 1.5 cm.; D.A.	0	0	0	3
42	3 yrs.	D.A. "widely patent"	0	0	0	1
43	3 yrs.	I.V.; I.A.; D.A.	0	0	0	1
44	3 yrs.	I.V. septum absent; I.A.	0	3	1	3
45	3½ yrs.	I.V. 1.2 cm.; I.A. 1.8 cm.; overriding aorta	1	2	1	0
46	4¾ yrs.	Ductus "probe patent"	0	0	0	1
47	6 yrs.	I.V. 1.0 cm.	1	2	2	0
48	8 yrs.	Foramen primum defect "large"	0	2	1	2
49	9 yrs.	I.V. septum absent; D.A. 0.3 cm.; Trans.	3	3	3	0
50§‡	13 yrs.	I.V. "large"; D.A.; I.A.	2	3	3	3
51	14 yrs.	I.A. 2 cm.; Trans.	1	3	3	0
52‡	15 yrs.	D.A.	3	3	2	0
53	16 yrs.	I.V. 1.5 cm.; D.A. 0.4 cm.; Trans.	2	3	3	0
54	21 yrs.	D.A. 0.5 cm.	0	1	1	0
55‡	26 yrs.	D.A.	1	2	3	0
56‡	26 yrs.	D.A. 0.7 cm.	3	3	3	0
57§†	31 yrs.	I.A. 1.5 cm.	3	3	3	0
58	33 yrs.	I.V. 0.6 cm.	0	1	1	0
59‡	36 yrs.	D.A.	3	3	3	0

* I.V. is interventricular septal defect; D.A. is ductus arteriosus; I.A. is interatrial septal defect; Trans. is transposition of the aorta and pulmonary artery.

† Grading system in text.

‡ Source for pulmonary emboli present.

§ Gross atherosclerotic plaques in elastic arteries.

sites[13] and must be considered here. The differences which make these groups useful in this study are summarized in table 1.

MATERIAL

We studied the autopsy material from 59 cases of congenital cardiac anomalies which would be expected to produce a shunt of blood from the left to the right side of the heart (table 2). No patients less than 3 months of age are included in this report because arterial intimal lesions were not encountered below that age. These 59 cases include all such patients over 1 year of age in the files of the Department of Pathology of Washington University and, in the age group 3 months to 1 year, all such individuals autopsied from 1944 to 1954. Patients under 1 year of age autopsied prior to 1944 were not included because this would have unduly weighted our material with infants.

Two groups of controls were established. In the first group were 31 patients 3 months to 38 years of age with pulmonary valvular or infundibular stenosis. All except one had an associated septal defect (table 3). Cases of pulmonary stenosis were eliminated if there was present any anomalous communication between aorta and pulmonary artery or if the patient had been subjected to a shunting operation longer than four days prior to death, because they were too complex hemodynamically to be readily classified.

A second control group (table 4) was composed of 39 autopsies of patients ranging from 3 months to 39 years of age that had no demonstrable cardiovascular abnormalities and no evidence of chronic pulmonary or generalized thrombotic disease. These cases were selected consecutively by age from the recent autopsy material and will be referred to in this paper as "normal" controls.

Material studied from these three groups of cases consisted of the blocks of lung tissue taken routinely at autopsy and embedded in paraffin. In a few cases additional tissues that had been preserved in formalin were extensively recut, and they established that the changes were sufficiently uniform and widespread to be represented in the routine sections. The lung sections from all were stained with Verhoff-van Gieson or aldehyde fuchsin-van Gieson-iron hematoxylin. These elastic and connective tissue stains were found necessary for detailed study of lesions. Paraffin sections from selected cases were stained by the periodic acid-Schiff leukofuchsin technique, with toluidine blue and with Weigert's fibrin stain. Oil red O stains for lipids were done on sections cut with the freezing microtome from selected cases. All of these stains

TABLE 3.—*Congenital Cardiac Anomalies with Pulmonary Stenosis*

Case No.	Age	Microscopic thrombi in pul. arteries*	Fibrous intimal thickening in pul. arteries and arterioles*	
			Severity	Frequency
1	3 mos.	0	0	0
2	3 mos.	0	0	0
3	4 mos.	0	0	0
4	4½ mos.	0	0	0
5	5 mos.	0	0	0
6	6 mos.	0	3	1
7	6 mos.	1	0	0
8	8 mos.	0	1	1
9	10 mos.	1	1	2
10	12 mos.	0	0	0
11	12 mos.	0	0	0
12	12 mos.	0	0	0
13	15 mos.	0	0	0
14	17 mos.	0	2	1
15	20 mos.	0	0	0
16	20 mos.	0	0	0
17	20 mos.	0	1	2
18	20 mos.	1	0	0
19†	2 yrs.	3	2	1
20†	2½ yrs.	3	2	3
21	4 yrs.	3	3	2
22	4½ yrs.	2	2	2
23	7 yrs.	0	1	3
24†	8 yrs.	1	1	2
25	10 yrs.	0	0	0
26	14 yrs.	1	3	2
27	16 yrs.	0	1	1
28†	17 yrs.	1	2	3
29	19 yrs.	3	3	3
30†	20 yrs.	3	2	3
31	38 yrs.	0	2	3

* Grading system in text.

† Source for pulmonary emboli present.

TABLE 4.—*"Normal" Control Series*

Number	Age	Thrombi*	Fibrous Intimal Thickening*	
			Severity	Frequency
1	3 mos.	0	0	0
2	4 mos.	0	0	0
3	4 mos.	0	0	0
4	5 mos.	0	0	0
5	6 mos.	0	0	0
6	6 mos.	0	0	0
7	7 mos.	0	0	0
8	7 mos.	0	0	0
9	8 mos.	0	0	0
10	10 mos.	0	0	0
11	12 mos.	0	0	0
12	2 yrs.	0	0	0
13	3 yrs.	0	0	0
14	5½ yrs.	0	0	0
15	8½ yrs.	0	0	0
16	9½ yrs.	0	1	1
17	10 yrs.	0	0	0
18	12 yrs.	1	1	1
19	14 yrs.	1	0	0
20	15 yrs.	1	0	0
21	15 yrs.	0	0	0
22	16 yrs.	0	0	0
23	20 yrs.	0	0	0
24	23 yrs.	0	1	1
25	23 yrs.	0	2	1
26	25 yrs.	0	0	0
27	25 yrs.	0	2	1
28	27 yrs.	0	0	0
29	28 yrs.	2	0	0
30	29 yrs.	0	0	0
31	30 yrs.	0	1	3
32	31 yrs.	2	1	3
33	32 yrs.	0	1	1
34	32 yrs.	0	1	3
35	33 yrs.	0	1	3
36	35 yrs.	0	2	3
37	35 yrs.	0	1	3
38	39 yrs.	0	1	1
39	39 yrs.	0	0	0

* Grading system in text.

are as described by Lillie,[14] except for minor modifications. The aldehyde fuchsin-van Gieson-iron hematoxylin stain is simply a combination of these three stains which is technically easier to perform and differentiates fibrous tissue, elastic tissue and muscle as satisfactorily as does the Verhoff-van Gieson method. This combination of stains was devised by Mr. Vernon Fischer of our laboratory.

OBSERVATIONS

Histopathology

Although the frequency and severity of intimal lesions varied somewhat in the different groups of cases, as will be described later, no distinguishing characteristics between individual lesions could be detected. In individuals with left-to-right shunt or pulmonary stenosis and in the normal controls, comparable lesions had the same structural and histochemical features. The following descriptions of specific types of lesions will therefore apply to all types of cases studied.

Large muscular arteries and elastic arteries were infrequent in the tissue sections as most of the tissue blocks had been taken from the periphery of the lungs. The lesions described were found principally in small muscular arteries and arterioles.

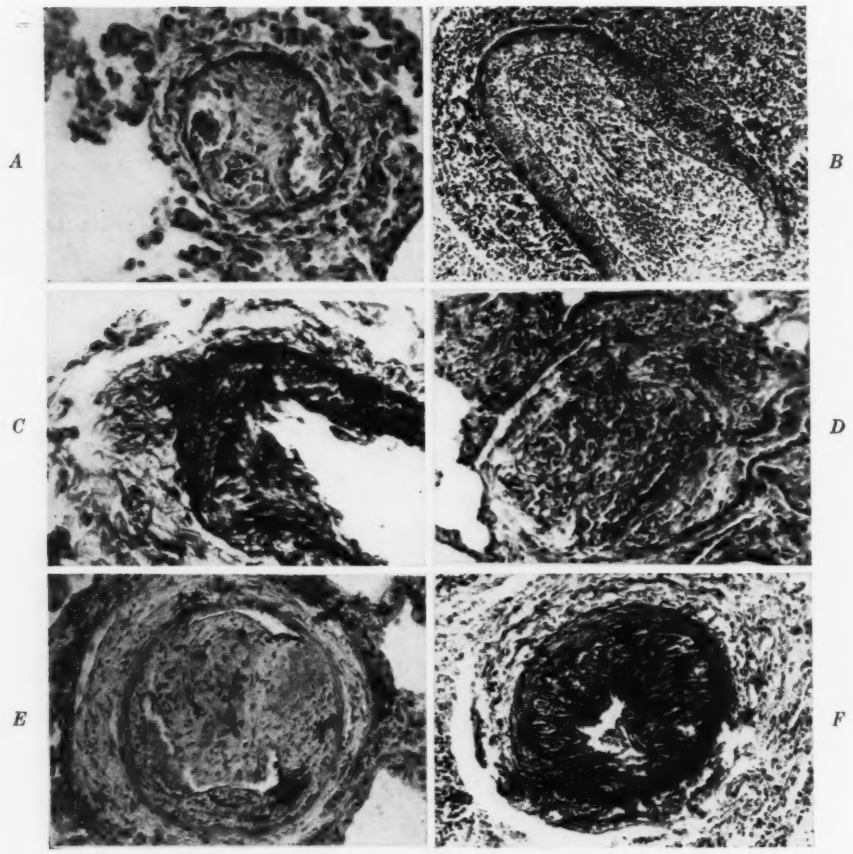

FIG. 1*A*, pulmonary stenosis case 8. A clearly recognizable organized and recanalized thrombus in a small pulmonary artery (Aldehyde fuchsin-van Gieson-iron hematoxylin × 270). *B*, left-to-right shunt case 31. A muscular artery with an organizing thrombus occluding its lumen. An inflammatory cell infiltrate extends through the muscle wall into the adventitia (Verhoff-van Gieson × 120). *C*, left-to-right shunt, case 27. Beneath the eccentric fibrous intimal lesion the internal elastic membrane is interrupted (Verhoff-van Gieson × 370). *D*, left-to-right shunt, case 40. The multiple devious endothelial lined channels resemble those seen in hemangiomas and arteriovenous aneurysms of glomus type. The original vessel wall is not visible (Verhoff-van Gieson × 120). *E*, pulmonary stenosis case 20. An organizing thrombus within a small muscular artery. Throughout much of the thrombus there is finely dispersed fat seen here as black to gray dots (Frozen section stained with Oil Red O and hematoxylin × 150). *F*, pulmonary stenosis case 6. An almost concentric fibrous intimal lesion (Aldehyde fuchsin-van Gieson-hematoxylin × 150).

Thrombi: A "clearly recognizable thrombus", as defined for this study, was any occlusive or partially occlusive lesion which still contained fibrin (fig. 3*A*) or had multiple lumina indicating recanalization (fig. 1*A*). The rare fibrous lesions projecting into the arterial lumina at approximately right angles to the walls were also classified as organized thrombi.

Occasionally there was a marked acute inflammatory reaction in the arterial wall (fig. 1*B*) in sections in which recent thrombi were demonstrated. Eosinophils were absent in the infiltrate, and the picture was similar to that produced in the pulmonary arteries of rabbits by intravenous injection of blood clot.[3,4]

Beneath older organizing thrombi, the media was frequently thinned or even absent, and occasionally vessel walls could not be demon-

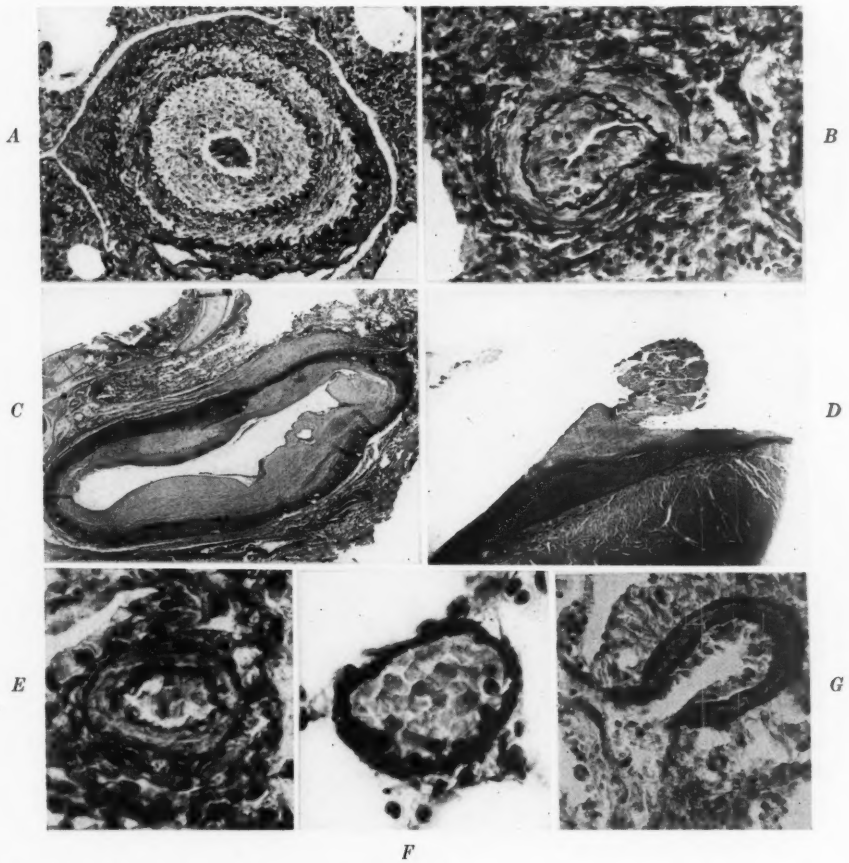

FIG. 2*A*, left-to-right shunt case 31. A concentric fibrous intimal lesion (Verhoff-van Gieson × 95). *B* left-to-right shunt case 44. An almost concentric fibrous intimal lesion in a small muscular artery with marked luminal narrowing (Verhoff-van Gieson × 320). C, left-to-right shunt case 57. An encircling atherosclerotic lesion in an elastic artery. Lesions in elastic arteries were uncommon (Aldehyde fuchsin-van Gieson-hematoxylin × 7). *D*, pulmonary stenosis case 20. A potential source for pulmonary emboli. This small mural thrombus is on the right ventricular endocardium near the pulmonary conus (Aldehyde fuchsin-van Gieson-hematoxylin × 12). *E*, left-to-right shunt case 32. A muscular arteriole. This was classified as grade 3 medial hypertrophy (Verhoff-van Gieson × 750). *F*, "normal" control, case 14. A normal pulmonary arteriole or venule. There is a single elastic coat (Aldehyde fuchsin-van Gieson-hematoxylin × 750). *G*, Pulmonary stenosis, case 21. Normal arterioles arising from a small muscular artery. Finding such an arteriole in continuity with a recognizable muscular artery is the only absolute method of distinguishing a normal arteriole from a venule (Aldehyde fuchsin-van Gieson-hematoxylin × 340).

strated around recanalized thrombi (fig. 1*D*). The latter, as pointed out by Rich,[7] have the superficial appearance of tiny hemangiomata.

Histochemical tests for stainable lipid revealed fine droplets and occasional larger globules of fat dispersed through the thrombi, with the most prominent collections in the unorganized portion, enmeshed in the fibrin (fig. 1*E*).

Fibrous Intimal Thickening: The presence of any fibrous tissue within the intima overlying the internal elastic membrane is considered abnormal[15] and was classified as fibrous intimal thickening unless the morphology conformed

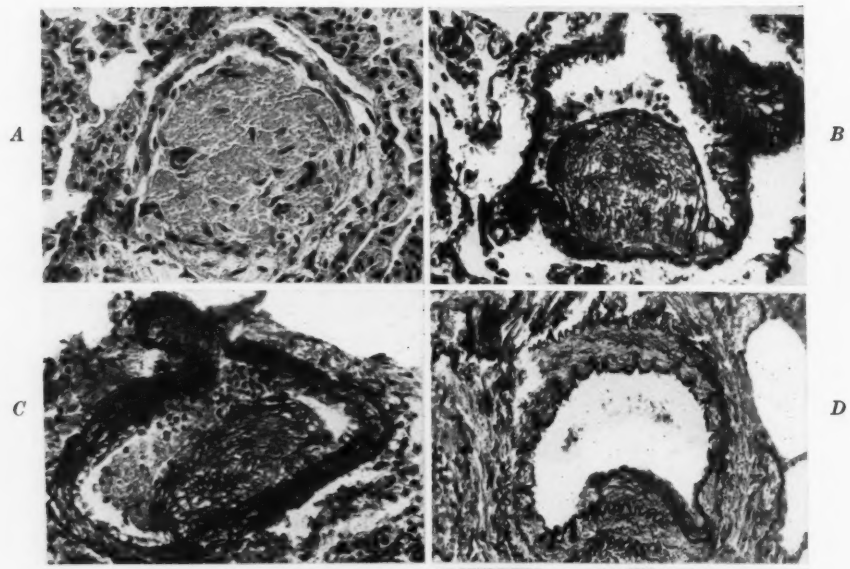

FIG. 3*A*, pulmonary stenosis case 20. A recent fibrin thrombus in a small muscular artery. There is beginning separation of the thrombus from the vessel wall (Hematoxylin and eosin × 270). *B*, pulmonary stenosis case 28. This lesion has a contour suggesting that of an original occluding thrombus which has contracted. The fibrous tissue is loose. In the center of the lesion is a small amount of dark granular material which may be remaining fibrin (Periodic acid-Schiff × 220). *C*, pulmonary stenosis case 22. This fibrous intimal lesion is flattened more than that in Fig. 15 and no trace of residual fibrin remains (Aldehyde fuchsin-van Gieson-hematoxylin × 220). *D*, left-to-right shunt case 49. In this lesion the fibrous tisue is more dense and elastic fibers are present (Verhoff-van Gieson × 125). *E*, pulmonary stenosis case 22. This lesion is even more flattened, dense and collagenized (Aldehyde fuchsin-van Gieson-hematoxylin × 210). *F*, pulmonary stenosis case 24. A mural thrombus in a small muscular artery. Organization of such thrombi could produce focal fibrous intimal lesions along the course of an artery (Aldehyde fuchsin-van Gieson-hematoxylin × 320).

to the criteria established above for clearly recognizable thrombi. Using these arbitrary criteria, most lesions could be readily classified, although the dividing line was not sharp.

In almost every case showing fibrous intimal thickening, both eccentric and concentric lesions were found. Arteriolar fibrous intimal thickening was more often concentric, and lesions of the arteries were sometimes concentric (figs. 1*F*, 2, *A* and *B*) but more often eccentric (fig. 3*E*).

Grossly demonstrable atherosclerotic plaques in large arteries were rare (fig. 2*C*). Lipid stains revealed droplets of fat trapped within some of the areas of fibrous intimal thickening in the selected lung sections stained with oil red O.

Thinning of the media beneath fibrous intimal plaques was frequently present, especially beneath the larger ones, and was more apparent beneath the eccentric fibrous lesions as the media could be compared with that of the opposite, normal vessel wall. Over these areas of definite medial thinning the internal elastica was usually interrupted (fig. 1*C*).

Comparative Data Regarding Incidence, Frequency and Severity of Lesions

Fibrous Intimal Thickening: We were surprised to find that the incidence of fibrous intimal thickening in cases with left-to-right shunt and in cases with pulmonary stenosis was almost the same, 46 and 55 per cent, respectively. The cases of each group (left-to-right shunt, pulmonary stenosis and normal control) were then broken down into age-groups. In each age-group the incidence of fibrous intimal thickening was similar for the two abnormal groups (left-to-right shunt, pulmonary stenosis). The incidence increased progressively with the age of the patients. In the age-groups over 10 years, the incidence was 100 per cent in both abnormal groups. In the age groups under 20, the incidence was much higher in the patients with either type of congenital cardiovascular anomaly than in the "normal" controls (table 5).

The frequency and severity of the lesions were then compared in the two abnormal groups. Frequency was classified "1" if an average of one to three vessels showing fibrous intimal thickening were found on each tissue section, "2" if four to six were found, and "3" if more. In many of those graded 3 almost every vessel showed lesions. The tissue sections were of comparable size in the different groups.

The severity of the intimal thickening was graded by each investigator independently with similar results. In order to obtain results that were as nearly precise as possible, direct measurements of the lesions were attempted. If sufficient numbers of relaxed vessels cut in direct cross section could have been found, this method would have been ideal. However, the vast majority of vessels showed some degree of contraction and were cut at an angle, so that this method was soon abandoned for more frankly subjective but probably more accurate grading. Fibrous intimal thickening of elastic and muscular arteries was considered grade 1 if the intima was definitely thickened but less than the thickness of the media, grade 2 if equal in thickness to the media and grade 3 if greater. In the arterioles, normally without media, the grade was based on narrowing of the diameter of the original lumen as indicated by the internal elastica (less than one-fourth, grade 1; one-fourth to one-half, grade 2; or over one-half, grade 3). In tabulating the final data, arterioles were not considered separately as they never showed changes without similar findings in small arteries. In general, the changes were more prominent in the small arteries.

For further comparison of these two abnormal groups it was decided to restrict ourselves to the age-group 1 through 20 years, since lesions were very frequent in this age-group whereas "normal" controls of this age showed very few lesions. In this age-group were 18 cases of pulmonary stenosis and 23 cases of left-to-right shunt.

On averaging the frequency of lesions in each of the two abnormal groups (age-group 1 through 20 years) almost identical figures were obtained, 2.1 for cases of pulmonary stenosis and 2 for left-to-right shunts. However, the average severity of the lesions was grade 1.9 for those having pulmonary stenosis and grade 2.6 for those with left-to-right shunt. On plot-

TABLE 5—*Incidence of Fibrous Intimal Thickening by Age*

	1 year and less		1 through 10 yrs.		11 through 20 yrs.		21 to 40 yrs.	
	No. of cases	%	No. of cases	%	No. of cases	%	No. of cases	%
Pulmonary stenosis	3 of 12	25	8 of 13	62	5 of 5	100	1 of 1	100
Left-to-right shunt	7 of 30	23	10 of 19	55	4 of 4	100	6 of 6	100
Normal Control	0 of 11	0	1 of 6	17	1 of 6	17	11 of 16	70

ting the distribution of grades in the two groups, the difference was found to be statistically significant (chi square test, 5 per cent level). However, the grading was to a great extent subjective.

Therefore, the only difference detected between the two abnormal groups was the greater severity of fibrous intimal thickening of small arteries and arterioles in the cases with left-to-right shunt.

Thrombi: In 39 per cent of patients with pulmonary stenosis and in 25 per cent of patients with left-to-right shunt thrombi were demonstrated in the pulmonary arteries. This incidence in pulmonary stenosis is much less than the percentage reported by Rich,[7] which is in part explained by the fact that more of our cases were less than one year of age and in some of his patients dying in the postoperative period, there were only recent thrombi. In all of our cases in which there were thrombi, some were organizing.

The incidence of thrombi increased with the increasing age of the patients. In the age-group 1 through 20 years, thrombi were encountered in 56 per cent of those with pulmonary stenosis and in 44 per cent of those with left-to-right shunt. In such small groups, we consider these figures essentially equal. The frequency of thrombi in each case was graded. An average of one to three per tissue section was "1", four to six was "2", and more "3". The average frequency of thrombi in the age-group 1 through 20 years was similar (1.9 and 2.1) in the two abnormal groups (left-to-right shunt and pulmonary stenosis). In "normal" controls in the age-group 1 through 20 years the incidence of thrombi (25 per cent) was less than in either abnormal group and the average frequency of thrombi (1.0) was much less.

Association of Thrombi and Fibrous Intimal Thickening: In every case of left-to-right shunt in which thrombi were found there was associated fibrous intimal thickening. In all but two of the cases of pulmonary stenosis in which thrombi were found there was also associated fibrous intimal thickening.

By the reverse comparison, that is, the incidence of thrombi in the cases with fibrous intimal thickening, almost identical figures were obtained for the age-group 1 through 20 years in the two abnormal series; 70 per cent (pulmonary stenosis) and 71 per cent (left-to-right shunt), both being very high incidences.

Sources for Emboli: Although no special search for sources of pulmonary emboli was made at autopsy of these cases, a surprising number of possibilities were described in the autopsy protocols (tables 2 and 3, footnotes). In five patients with pulmonary stenosis there were mural thrombi or vegetations within the right side of the heart (fig. 2*D*) and in all of these patients thrombi and fibrous intimal thickening were prominent in the pulmonary arteries. Of seven cases with left-to-right shunt having a source for pulmonary emboli, three had sources within the heart, three had vegetations on a patent ductus arteriosus, and one had hepatic vein thrombi. In the pulmonary arteries of all seven, thrombi and advanced fibrous intimal thickening were present. These 12 patients with potential sources for emboli represented approximately one-half of the number with thrombi in the pulmonary arteries.

Type of Anomaly: The incidence, frequency and severity of lesions in patients with left-to-right shunt have no constant relation to the types of anomalies present in this series (table 2).

Pulmonary Hypertension: Data obtained from catheterization studies were not available on the patients in this study. Even large left-to-right shunts may not necessarily be accompanied by pulmonary hypertension.[11] However, we obtained evidence concerning the effects of pulmonary hypertension by two indirect approaches.

Although direct measurement of pressure is the only absolute method for determination of pulmonary hypertension, its presence from birth is presumptively indicated by the persistence of thick, muscular arteriolar media similar to the media of the normal pulmonary arterioles of the new-born and of systemic arterioles throughout life.[16, 17] This persistence of muscular arterioles was found only in the young patients (table 2).

The thickness of arteriolar media present was graded 0, 1, 2 and 3; the highest grade indicates pulmonary arteriolar medial thick-

ness equalling or exceeding that of systemic arterioles (figs. 2E, F and G). Of special interest were the cases of left-to-right shunt without intimal change but with definite morphologic evidence indicating pre-existing pulmonary hypertension. There were six patients (cases No. 30, 33, 34, 37, 38 and 42), ages 1 to 3, with marked (grade 3) medial hypertrophy and no intimal lesions. Patients over three years of age were not suitable for this type of comparison because medial hypertrophy was so rare (3 of 15 cases) and fibrous intimal thickening so frequent (14 of 15 cases). It is interesting that Welch and Kinney[18] in a similar study of 67 cases with left-to-right shunt reported the absence of muscular hypertrophy in every case. We have no explanation for this discrepancy.

The second method of approach regarding the effects of hypertension was the comparison of the left-to-right shunt group with the pulmonary stenosis group. The presence of large numbers of obstructive arterial lesions in individuals with a normal circulation will result in pulmonary hypertension.[19] Even less obstruction should be required for production of hypertension in the presence of a left-to-right shunt. On the other hand, in the presence of pulmonary stenosis and a septal defect, the pulmonary arterial pressure should remain low even in the presence of large numbers of obstructive lesions.

Since most of our patients in the age-group 1 through 20 years with left-to-right shunt showed multiple obstructive lesions, we can assume that as a group they had a higher pulmonary arterial pressure than the corresponding pulmonary stenosis group. As previously stated, the incidence and frequency of fibrous intimal thickening in the 2 groups are similar. The severity of lesions was significantly greater in the left-to-right shunt group (tables 2, 3 and 4).

Discussion

Association of pulmonary arteriosclerosis and thrombi: Pulmonary arteriosclerosis was found to be common in patients with either left-to-right shunt or pulmonary stenosis. In our cases there was a striking association of fibrous intimal thickening characteristic of arteriosclerosis with pulmonary arterial thrombi regardless of the type of congenital anomaly present. This close association of pulmonary arteriosclerosis and thrombi suggests that one resulted from the other. Since most of the clearly recognizable thrombi were found in vessels with no preexisting arteriosclerosis, it is unlikely that the arteriosclerotic lesions led to the formation of thrombi. Therefore, it is necessary to consider the reverse possibility, which is that the arteriosclerotic lesions resulted from the thrombi.

Role of thrombi in the production of pulmonary arteriosclerosis: The arteriosclerotic lesions may actually be an unusual form of organized thrombi or the lesions may result from hemodynamic alterations produced by the thrombotic vascular obstructions. In support of the former possibility, we were able to demonstrate transition stages from clearly recognizable thrombi to arteriosclerotic lesions.

The idea that pulmonary arteriosclerotic lesions can arise directly from the organization of thrombi is a radical one but a great deal of supporting evidence has been accumulated in recent years. Fibrous intimal thickening of the pulmonary arteries characteristic of pulmonary arteriosclerosis has been produced in experimental animals by repeated intravenous injection of thrombi.[2, 6] The stages of development from thrombi to arteriosclerotic lesions have been demonstrated by sacrificing the animals at suitable intervals.

In our human cases, we searched for evidence indicating that a similar sequence of events had occurred. It is quite possible that most thrombi in pulmonary vessels lyse completely leaving no permanent change in the vessel walls. It is widely recognized that other thrombi are transformed into fibrous tissue through which pass multiple devious blood channels and we found many such organized, recanalized thrombi in our cases. However, we found evidence that other, less widely recognized forms of organization occurred resulting in fibrous intimal thickening characteristic of arteriosclerosis. Presentation of this evidence requires the introduction of additional data into the discussion at this point.

One theoretical form of organization of

thrombi resulting in arteriosclerotic lesions in small branches of the pulmonary arterial tree is illustrated in the series of selected lesions shown in figures 3*A* through 3*E*. Figure 3*A* shows a small muscular pulmonary artery containing a thrombus composed largely of fibrin but with a few enmeshed erythrocytes. Early organization has already begun as indicated by scattered fibroblasts within the thrombus. There is beginning contraction of the thrombus with separation from the arterial wall on one side. Endothelial cells have grown out to partially cover the thrombus at the site of separation. The penetration of new capillaries from the vessel wall which is characteristic of the organization of larger thrombi is seldom seen in small thrombi such as this one. Nutrition of cells within the thrombus is presumably accomplished by diffusion. Lipid stains on frozen sections of other thrombi of similar apparent age have shown considerable stainable lipid within the thrombus.

Figure 3*B* shows a later stage in the organization of a thrombus. There has been further contraction but the rounded contour of an original occluding thrombus is still apparent. Many more fibroblasts are present, and between these there is a prominent fibrillar substance that stains deep purple with the aldehyde fuchsin-vanGieson-hematoxylin, in contradistinction to the adventitial collagen which stains red. A deeper section of the same lesion stained intensely with PAS, suggesting that some fibrin is still present. The intercellular substance in some similar lesions is metachromatic after toluidine blue staining. Lipid stains frequently show enmeshed fat droplets.

Figures 3*C* and 3*D* show lesions with similar characteristics that have apparently undergone further contraction. Figure 3*E* is of a still later stage, in which the connective tissue has been largely transformed to dense collagen.

There may be numerous other variations in the evolution of such lesions. An occluding thrombus may divide into two parts with contracture and result in two arteriosclerotic lesions. Concentric lesions (figs. 1*F* and 2*A*) may result from central recanalization of an occluding thrombus. Eccentric lesions may develop directly by the organization of mural thrombi such as that shown in figure 3*F*.

Role of hypertension in the production of pulmonary arteriosclerosis: The possibility that fibrous intimal thickening of the pulmonary arteries can be produced by hypertension alone cannot be excluded. However, similar intimal lesions were present in patients with either left-to-right shunt or pulmonary stenosis. Since patients with pulmonary stenosis are generally expected to have low or normal, rather than high, pulmonary arterial pressures, hypertension may not be a necessary factor in the production of fibrous intimal thickening.

The severity of intimal lesions was greater in the cases with left-to-right shunts than in those with pulmonary stenosis. This difference in degree suggests that hypertension or increased rate of flow increases the fibrous intimal response to thrombi, acting as an accessory but not essential factor in the production of fibrous intimal thickening.

Evidence that pulmonary hypertension alone does not readily produce arteriosclerosis is found in our data concerning the patients in the first three years of life. Arteriosclerotic lesions were seen in seven patients less than 1 year of age, and the lesions were severe in one patient 9 months of age in which numerous thrombi were also present. In only two of these cases was there morphologic evidence suggesting the presence of pulmonary hypertension since birth. On the other hand, there were six cases, ages 1 to 3 years, in which morphologic evidence of pulmonary hypertension was present and arteriosclerosis could not be demonstrated.

Role of rate of blood flow in the production of pulmonary arteriosclerosis: Increased rate of pulmonary blood flow was probably present in most of the cases of left-to-right shunt, at least prior to the terminal illness. It was impossible in this study to accurately evaluate changes in rate of flow as a factor in producing pulmonary arteriosclerosis. If we assume the rate was generally increased in patients with left-to-right shunt and decreased in pulmonary stenosis, we must conclude that increased rate of flow could not be the primary factor. However, recent experimental studies of Liebow[26] have shown

that an increased pulmonary blood flow can exist in the presence of pulmonary stenosis through expanded anastomoses between bronchial and pulmonary arteries. How frequently the pulmonary blood flow in cases with pulmonary stenosis is in fact raised to or above normal by this collateral supply is not known.

Origin of thrombi: The incidence of pulmonary arterial thrombi is approximately the same in patients having congenital heart disease with either left-to-right shunt or pulmonary stenosis. Polycythemia was present in all but one of the cases of pulmonary stenosis from which erythrocyte counts were available and absent in most of the patients with left-to-right shunt. This fact suggests that polycythemia is not of primary importance in the production of thrombi in patients with these anomalies. Furthermore, since it can be reasonably assumed that the rate of flow through the pulmonary arteries was much greater in patients with left-to-right shunt than in those with pulmonary stenosis, rate of flow also must not have been of primary importance in the production of thrombi. The number of cases in which obvious sources for emboli were demonstrated suggests that these pulmonary arterial thrombi may all be of embolic origin. More thorough autopsy examination of such patients may reveal an even higher incidence of sources.

Arteritis: The acute inflammatory lesions of arterial walls seen occasionally in this study (fig. 1*B*) were considered to indicate a reaction to an intraluminal thrombus, and could have been responsible for some of the destruction of media found beneath the plaques. These inflammatory lesions were similar to some of those reported by others as examples of pulmonary polyarteritis nodosa.[11] However, lesions in our cases lacked the distinctive features of polyarteritis. Furthermore, the similarity of the lesions in our cases to those produced in experimental animals[3] by emboli enables us to eliminate polyarteritis from serious consideration.

Summary and Conclusions

Thromboembolism, pulmonary hypertension and increased rate of flow have been assessed as factors in the production of pulmonary arteriosclerosis. A study was made of autopsy records and tissue sections from 59 cases of congenital heart disease with anomalies permitting shunting of blood from the systemic to the pulmonary circulation (left-to-right shunt), 31 cases with pulmonary stenosis and septal defect (mostly tetralogy of Fallot) and 39 "normal" controls. The following conclusions were reached.

1. Pulmonary arteriosclerotic lesions are very frequent in congenital heart disease whether a left-to-right shunt or pulmonary stenosis is present.

2. Pulmonary arterial thrombi are similarly frequent (25 and 39 per cent) in cases with left-to-right shunt or with pulmonary stenosis.

3. The high (approximately 70 per cent) association of thrombi and arteriosclerosis, regardless of the type of anomaly present, indicates that organization of thrombi may be the primary factor in these cases.

4. Evidence for the embolic origin of the pulmonary arterial thrombi is presented.

5. A series of lesions is presented indicating the probable stages in the transformation of a fresh thrombus to an arteriosclerotic lesion.

6. It is unlikely that hypertension and increased rate of pulmonary blood flow are primary factors in the production of pulmonary arteriosclerosis. But the severity of arteriosclerotic lesions is greater in cases with left-to-right shunt than in those with pulmonary stenosis, suggesting that increased pressure and blood flow in these vessels may be etiologic factors of accessory importance.

Summario in Interlingua

Thromboembolismo e hypertension pulmonar ha essite designate como factores in le production de arteriosclerosis pulmonar. Nos ha executate un studio de protocollos autoptic e de histosectiones ab 59 casos de congenite morbo cardiac con anomalias que permitteva le derivation del sanguine ab le circulation major verso le circulation minor e ab 31 casos de stenosis pulmonar con defecto septal. Arteriosclerosis pulmonar esseva commun e de frequentia equal in le duo gruppos, lo que indica que hypertension non es un factor necessari. Il existeva un alte correlation inter

le presentia de thrombos del arteria pulmonar e arteriosclerosis pulmonar.

ACKNOWLEDGMENT

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REFERENCES

[1] DUGUID, J. B.: The arterial lining. Lancet **2:** 207, 1952.

[2] HARRISON, C. V.: Experimental pulmonary arteriosclerosis. J. Path. & Bact. **60:** 289, 1948.

[3] WARTMAN, W. B., JENNINGS, R. B. AND HUDSON, B.: Experimental arterial disease. I. The reaction of the pulmonary artery to minute emboli of blood clot. Circulation **4:** 747, 1951.

[4] MUIRHEAD, E. E. AND MONTGOMERY, P. O'B.: Thromboembolic pulmonary arteritis and vascular sclerosis. Arch. Path. **52:** 505, 1951.

[5] HEARD, BRIAN E.: An experimental study of thickening of the pulmonary arteries of rabbits produced by the organization of fibrin. J. Path. & Bact. **64:** 13, 1952.

[6] BARNARD, P. J.: Pulmonary arteriosclerosis and cor pulmonale due to recurrent thromboembolism. Circulation **10:** 343, 1954.

[7] RICH, ARNOLD R.: A hitherto unrecognized tendency to the development of widespread pulmonary vascular obstruction in patients with congenital pulmonary stenosis (Tetralogy of Fallot). Bull. Johns Hopkins Hosp. **82:** 389, 1948.

[8] FRIEDBERG, C. K.: Diseases of the Heart. Philadelphia, W. B. Saunders, 1949, p. 638.

[9] STEWART, H. L. AND CRAWFORD, B. L.: Congenital heart disease with pulmonary arteritis. Am. J. Path. **9:** 637, 1933.

[10] OLD, J. W. AND RUSSELL, W. O.: Necrotizing pulmonary arteritis occurring with congenital heart disease: Report of a case with necropsy. Am. J. Path. **26:** 789, 1950.

[11] EDWARDS, J. E.: Congenital malformation of the heart and great vessels. *In*, Pathology of the Heart, S. E. Gould, ed. Springfield, Charles C Thomas, 1953.

[12] BING, R. J., VANDAM, L. D. AND GRAY, F. D., JR.: Physiological studies in congenital heart disease; results of preoperative studies in patients with tetralogy of Fallot. Bull. Johns Hopkins Hosp. **80:** 121, 1947.

[13] DOCK, W.: Blood flow, blood pressure and intimal thickness as factors in localizing atheroma formation. *In* Factors Regulating Blood Pressure. Josiah Macy, Jr., Foundation, New York, 1951, p. 129.

[14] LILLIE, R. D.: *Histopathologic Technic and Practical Histochemistry*. New York, Blakiston, 1954.

[15] BRENNER, O.: Pathology of the vessels of the pulmonary circulation. Arch. Int. Med. **56:** 457, 1935.

[16] VALENZUELA, C. T., TORIELLO, J. AND THOMAS, W. A.: Structural changes in intrapulmonary arteries exposed to systemic pressures from birth. Arch. Path. **57:** 51, 1954.

[17] GOODALE, F. AND THOMAS, W. A.: Primary pulmonary arterial disease with special reference to medial thickening of small arteries and arterioles. Arch. Path. **58:** 568, 1954.

[18] WELCH, K. J. AND KINNEY, T. D.: The effect of patent ductus arteriosus and of interauricular and interventricular septal defects on the development of pulmonary vascular lesions. Am. J. Path. **24:** 729, 1948.

[19] OWEN, W. R., THOMAS, W. A., CASTLEMAN, B. AND BLAND, E. F.: Unrecognized emboli to the lungs with subsequent cor pulmonale. New England J. Med. **249:** 919, 1953.

[20] LIEBOW, A. A., HARRISON, W. AND HALES, M. R.: Experimental pulmonic stenosis. Bull. Internat. A. M. Museums (Lab. Invest.) **31:** 1, 1950.

Exercise and Cardiac Work Response at High Altitude

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The response to treadmill exercise of the left ventricle of natives of the region of Morococha, Peru (elevation 14,900 feet), and of natives of the region of Lima, Peru (elevation 500 feet), was studied at the elevation where they had always lived. In both groups the external work of the left ventricle was effected by a combination of a large increase in cardiac output and a mild increase in systemic blood pressure. Stroke volume and stroke work were only mildly elevated since the heart rate was concurrently greatly increased. As a result, the increase in work of the left ventricle was largely accomplished by an increase in heart rate and to a lesser extent by an increase in stroke work. For comparable amounts of external work, the left ventricle of the native to high altitude and performing at high altitude responded with considerably greater effort than did the left ventricle of the native of low altitude performing at sea level. Some of the data may have approximated the maximum effort of which the normal left ventricle was capable.

THIS report is concerned primarily with attempts to measure the extent and adequacy of the response of the heart of man to the stress of chronic anoxia at high altitude. Although the native living at a high altitude undergoes considerable acclimatization by changes in his cardiovascular, respiratory, and hematologic systems,[1, 2, 3, 4, 5] the extent of adaptation by the heart in the resting condition and especially in the state of exercise has not been well defined or studied. Measurements of the effect of external work on dynamics of the heart have thus far been limited to determinations at sea level of cardiac output during heavy exercise[6, 7, 8, 9] and of cardiac work during light exercise.[10, 11, 12, 13] In the present study comparisons were made of the response of the left ventricle of the native indigenous to high altitude and living at high altitude, with the response of the heart of the sea level dweller at sea level during exercise on a treadmill at equivalent and at an approximation to maximal levels of muscular work.

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Methods and Procedures

Twenty-six male volunteers were studied either at Morococha, Peru (elevation 14,900 feet), or at Lima, Peru (elevation 500 feet). Of the 17 subjects studied at high altitude, 11 were natives of the region of Morococha who had not lived for any length of time at a significantly lower elevation; all were apparently in good health, and were, for the most part, engaged in mining activities. The remaining six subjects studied at the 14,900 foot altitude were normally inhabitants of sea level who had been living at Morococha for only six to eight weeks. Of the nine subjects studied at Lima, Peru, seven were medical students and two were sailors. The ages of the natives at high altitude varied from 19 to 38 years, the medical students from 22 to 28 years, and the sailors from 19 to 23 years.

For control measurements the subjects stood on a motor driven treadmill. The values obtained were not regarded as those from subjects at standing rest, since, without doubt, many were excited and stimulated by the unfamiliar procedures and the presence of strange personnel. Cardiac output was determined by the Evans blue dye-dilution method, using a continuously recording densitometer.[14, 15]

To facilitate sampling of arterial blood, a hyperextended wrist was immobilized in a plaster splint secured to a stationary arm rest. Moderate freedom of movement of the elbow was permitted. A 40 to 50 cm. length of polyethylene tubing was then passed into the basilic vein through a 15 or 17 gage thinwalled needle for dye injection. A 20 gage thinwalled needle was inserted into the radial artery, and after being securely taped to the wrist was connected by a three-way stopcock and a flexible coupling to the densitometer and to a strain gage for measurement of heart rate and mean radial

blood pressure. The subjects generally were given 2 ml. of heparin sodium (2000 units) intravenously to obviate clotting within the arterial needle. As an additional preventive measure, the needle was flushed with small quantities of saline between determinations of cardiac output. These procedures were effective and no difficulties were encountered with hematomas after removal of the needle. In some subjects a Douglas bag was connected to the mouthpiece for the measurement of expired gases and for the determination of total oxygen consumption. After control determinations were made of the hemoglobin, hematocrit, cardiac output, heart rate, systemic blood pressure, and oxygen consumption (2 to 3 minutes), the treadmill was started and the rate and duration of external work adjusted in an attempt to create a heavy cardiac work load. When the subject had been exercising at a constant rate of external work for a few minutes and was considered to be in a relatively steady state, determinations of the above parameters (except for the hemoglobin and hematocrit) were repeated. In two subjects in whom the initial rate of doing work was not exhausting, measurements were repeated at the same rate of treadmill exercise. In six other subjects measurements were repeated either at a considerably higher rate of external work on the treadmill and without interruption of it, or, after obtaining values believed to be the response of the heart to the maximum activity on the treadmill of which the subject was capable, the work load was abruptly decreased and observations were made at a lower level of cardiac activity. To attain the various levels of work by the heart, the subjects walked on the treadmill at rates varying from about 4 to 7 miles per hour; the duration of exercise varied from 3 to 10 minutes and the grade approximated either 11 or 20 per cent. The duration of exercise would seem to be adequate for a "steady state", since Donald has shown that the output and arteriovenous oxygen difference become quite constant in one minute.[9]

Typical patterns of densitometer curves from which the cardiac output values were calculated are illustrated in figure 1. The curves shown were obtained in the same native subject at Morococha at rest and during strenuous treadmill exercise. All calculations of cardiac output were done using calibration curves made with each individual's arterial blood. In the mountains, where the blood was unsaturated, calibration points (dilutions of dye and blood) were made and recorded with the densitometer without exposure to air to avoid changes in saturation.[16] Calculations of cardiac output, cardiac work, and stroke work were made as previously described,[17, 18] except that the cardiac work and stroke work were not corrected for the prevailing left ventricular end-diastolic pressure, which was not measured.

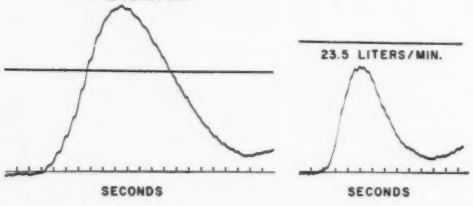

FIG. 1. Densitometer patterns from native at Morococha, Peru; on the left, during rest, and on the right, during heavy exercise.

RESULTS

Table 1 contains the original and calculated data from the three groups of subjects. Group 1 (natives at the altitude) and group 2 (medical students at sea level) are considered together. The natives at the altitude had the smaller body surface area and body weight, the latter averaging about 10 Kg. less than the other group. In the natives the hemoglobin varied from 17.7 to 24.3 with an average of 20.2 Gm. per 100 cc. Their hematocrits averaged 59.7 with high and low values of 71.5 and 51. Although in this group most values for hematocrit and hemoglobin were quite high and suggested chronic mountain sickness, all subjects were asymptomatic. At sea level the hematocrit and hemoglobin values were within normal limits. At the altitude of 14,900 feet at Morococha, Peru, all natives were chronically hypoxic. At this altitude (barometric pressure approximately 430 mm. Hg) the partial pressure of inspired oxygen is about 80 mm. Hg and the alveolar oxygen tension approximately 50 mm. Hg with an arterial oxygen saturation ranging from 75 to 86 per cent and a mean of approximately 81.5 per cent.[5] Despite this and because of his high hematocrit the mountain native generally has an elevated oxygen content of his blood.

The external work load of the high-altitude native on the treadmill averaged 589 Kg.M. per minute per square meter of body surface area with extremes of 490 and 749. These loads have been arbitrarily divided into two groups in table 1 to more clearly show the effect of varying external work load on cardiac response. In the medical students at sea level the work load considerably exceeded that in the mountain natives, ranging from 704 to 986 Kg.M per

TABLE 1. *Hemodynamic Studies During Rest and Exercise at Sea Level and at High Altitude*

Subject	Age	Wt. Kg.	S.A. M^2	Hb. Gm./ 100 cc.	Hct.	Tm. Work Kg.M/ min./M^2	Heart Rate Beats/ min.	M.B.P. mm. Hg	C.I. L./min./ M^2	C.W.I. Kg.M/ min./M^2	S.V.I. cc./min./ M^2	S.W.I. Gm.M/ min./M^2	Oxygen Consumption, L./ min./M^2
Group 1. Natives at 14,900 feet													
G. C.	19	56.5	1.57	17.7	54.0	0	72	100	3.73	5.07	52	70	0.138
						527	150	100	6.70	9.09	45	61	1.015
						527	180	126	6.80	11.66	38	64	
G. F.	20	55.5	1.53	17.9	56.0	0	60	90	3.47	4.24	58	71	0.173
						530	120	94	6.50	8.30	54	69	0.806
						530	120	100	5.97	8.10	50	67	
T. O.	29	58.0	1.55	23.5	68.0	0	90	116	3.34	5.26	37	59	0.172
						548	168	133	6.02	10.89	36	65	1.164
R. B.	38	69.5	1.75		67.0	0	96	111	8.14	12.29	85	127	0.166
						580	180	124	5.55	9.36	31	52	
J. M.	22	63.5	1.68	19.0	59.7	0	90	85	1.94	2.24	21	25	
						553	141	112	5.38	8.20	38	58	1.054
E. O.	20	53.6	1.47	24.1	61.3	0	87	85	3.70	4.28	43	50	0.178
						533	144	98	4.36	5.79	31	41	1.021
						707	157	99	6.38	8.60	41	54	
R. F.	19	52.5	1.55	18.1	55.5	0	90	102	1.71	2.37	19	27	0.228
						495	160	110	9.25	13.79	58	87	1.057
						657	180	102	13.74	19.05	76	105	
J. M. R.	22	50.5	1.51	18.4	56.0	0	79	116	3.96	6.24	50	80	0.524
						490	180	135	6.58	12.05	36	67	
						650	180	130	11.75	20.78	66	116	1.044
E. T.	19	62.5	1.69	19.6	51.0	0	68	99	4.20	5.66	62	83	0.161
						541	144	120	13.91	22.63	96	158	
						718	156	108	18.82	27.65	121	177	0.911
T. H.	31	66.0	1.71	24.3	71.5	0	90	114	8.13	12.61	91	141	0.187
						565	180	164	12.48	27.75	70	155	1.220
						749	180	164	20.82	46.43	116	258	
J. C.	26	56.5	1.56	19.8	56.3	0	96	96	4.15	5.41	44	56	0.158
						703	180	123	10.80	18.06	60	101	1.430
Averages													
Rest									4.22	5.97	51.1	71.7	0.209
Exercise 535 (490–580) Kg.M/min./M^2									7.5	12.3	48.6	78.7	1.048
Exercise 697 (650–749) Kg.M/min./M^2									13.7	23.4	80.0	135.2	1.128
Group 2. Medical students at sea level													
J. V.	28	77.7	1.86	16.7	49.5	0	100	119	2.44	3.90	24	30	
M. L.	22	69.5	1.86	16.4	48.5	0	67	95	2.38	3.07	35	46	
						737	180	113	8.25	12.68	46	70	1.06
J. R. F.	24	59.5	1.62	16.3	48.9	0	90	96	3.73	4.87	41	54	
						724	100	96	7.28	9.51	73	95	1.190
J. Ja.	22	63.5	1.73	16.0	48.8	0	75	89	2.32	2.80	31	38	
						725	178	114	9.76	15.14	55	85	1.350
J. J.	23	60.3	1.69	16.1	46.5	0	82	87	2.29	2.71	28	33	
						704	161	122	6.72	11.15	41	69	1.230
J. L. L.	27	64.5	1.70			0	70	83	2.60	2.94	37	42	
						986	180	111	7.53	11.37	42	63	1.680
J. I.	23	64.5	1.70	15.1	46.0	0	100	100	3.47	4.72	35	47	
						986	180	100	9.20	12.51	51	69	1.610
Averages													
Rest									2.75	3.57	33	41	
Exercise 810 (704–986) Kg.M/min./M^2									8.12	12.06	51	75	1.353

TABLE 1—*Continued*

Subject	Age	Wt. Kg.	S.A. M^2	Hb. Gm./ 100 cc.	Hct.	Tm. Work Kg.M/ min./M^2	Heart Rate Beats/ min.	M.B.P. mm. Hg	C.I. L./min./ M^2	C.W.I. Kg.M/ min./M^2	S.V.I. cc./min./ M^2	S.W.I. Gm.M/ min./M^2	Oxygen Consumption, L./ min./M^2
Group 3. Partially acclimatized sailors at 14,900 feet													
M.	23	54.5	1.51	17.8	50.0	0			3.64				0.156
									4.60				0.174
O. M.	19	68.0	1.74			0	90	102	2.87	3.97	32	44	
						290	130	116	5.41	8.51	41	66	
A. M.	19	61.0	1.65	18.0	55.4	0	110	92	1.81	2.27	16	21	
						273	140	105	2.85	4.06	21	30	
						545	180	109	7.27	10.77	41	60	
A. C.	22	76.5	1.86	18.1	55.9	0	115	100	2.73	3.71	24	32	
						602	170	130	6.84	12.09	40	72	
L. S.	19	64.5	1.70	15.9	54.5	0	90	102	3.02	4.19	34	47	0.253
						555	170	122	3.91	6.49	23	38	0.807
S. P.	20	71.0	1.78	18.4	55.2	0	100	87	4.01	4.75	40	47	
						584	160	114	6.47	10.04	40	63	
Averages													
Rest									3.24	3.78	29	38	
Exercise 572 (545–602) Kg.M/min./M^2									5.46	8.66	34	55	

Abbreviations used in table: S.A.: Surface Area; Hb.: Hemoglobin; Hct.: Hematocrit; Tm.: Treadmill; M.B.P.: Mean Blood Pressure; C.I.: Cardiac Index; C.W.I.: Cardiac Work Index; S.V.I.: Stroke Volume Index; S.W.I.: Stroke Work Index.

minute per square meter and averaging 810. This difference is perhaps explained in part by the fact that these students weighed on an average approximately 10 Kg. more than the high-altitude natives.

As might have been expected, considerable variation in hemodynamic response from individual to individual was found. It is doubtful that the mathematical precision of statistical analysis would add much to the meaning of this data. However, fully realizing the limitations of the measurements, some trends were apparent which are of interest.

The average control heart rates for the two groups (altitude natives and sea level medical students, respectively) were the same at 83 per minute. In all subjects, except for one native in the mountains and one medical student at sea level, the increase of the heart rate was large during exercise. Increases in rate tended to be greatest with the greatest treadmill activity; the average values for the two groups were 161 and 163 per minute.

The average resting values for the mean systemic blood pressure in the two groups (high altitude natives and sea level dwellers) were 101 and 96 mm. Hg. In contrast to the large increase in heart rate the increase in mean systemic blood pressure was generally mild in these groups during exercise, the highest values being 164 in a native at the altitude and 122 in a medical student at sea level. An occasional subject in each group showed no change or a slight reduction in mean blood pressure. The averages during exercise for the high-altitude natives and sea level subjects were 119 and 109 mm. Hg mean radial pressure, respectively.

The average control cardiac work index was higher in the group of mountain natives, in whom the value was 6 compared to 3.6 Kg.M. per minute per square meter in the other group. In two mountain natives in whom measurements were repeated at the same rate of treadmill exercise the values for cardiac work index (also cardiac index, stroke volume index, and stroke work index) were fairly constant indicating that in the period of two to four minutes a reasonably steady state for these parameters was obtained. With one exception values for cardiac index and cardiac work index increased as the level of treadmill activity was increased.

This was also true of stroke volume index and stroke work index in sea level subjects and in the majority of the natives at high altitude.

Keeping in mind the individual variations in the response of the cardiac index to exercise, for a lesser treadmill work load, the average value for cardiac index in the high-altitude native was somewhat greater than that of the sea level subject (9.5 versus 8.1 liters per minute per square meter, respectively). It is of interest also that when the work levels of the high altitude natives are broken down into groups, at work levels ranging from 490 to 580 Kg.M. per minute per square meter (average 535), the cardiac index averaged 7.5 L. per minute per square meter, while at 650 to 749 Kg.M. per minute per square meter (average 697), the cardiac index averaged 13.7 L. per minute per square meter. This contrasts with the average value of 8.1 L. per minute per square meter for sea level subjects working at rates varying from 704 to 986 Kg.M. per minute per square meter (average 810).

As a result of the large increase in cardiac output in all subjects and the mild increase of mean systemic blood pressure, the cardiac work index rose greatly with exercise. This was especially evident in the group of natives in whom the average value was 16 as compared to 12.1 Kg.M. per minute per square meter in the medical students, despite the fact that the natives were doing considerably less work on the treadmill. In the natives who were working at only 490 to 580 Kg.M. per minute per square meter the average cardiac work index was 12.3 Kg.M. per minute per square meter but in the natives exercising at 650 to 749 Kg.M. per minute per square meter (still less than in the medical students) the cardiac work index was 23.4 Kg.M. per minute per square meter. The possible influence of such factors as the difference in body type and weight in these two groups must be kept in mind; their importance in attempting to compare cardiac response to equivalent work loads is unknown.

At rest the stroke volume index of the natives in Morococha was higher with an average value of 51 compared to 33 cc. per minute per square meter in the group of medical students at sea level. From a combination of the competing mechanisms of a large increase of heart rate and cardiac output, the stroke volume index was only moderately increased with exercise. In that portion of the group of natives who were performing at an external work level (650 to 749 Kg.M. per minute per square meter) only moderately below that of the medical students, the average stroke volume index was 80 cc. per minute per square meter; in the natives who worked at a considerably lower rate (490 to 580 Kg.M. per minute per square meter) the stroke volume index of 49 cc. per minute per square meter approximated that of the sea level exercising student.

At rest the natives of Morococha had a considerably greater stroke work index than the sea level medical students. During exercise, as the result of a mild augmentation of stroke volume and systemic blood pressure, these values were increased, average figures being 97.5 and 75 Gm.M. per minute per square meter with the greater value being in the native at the altitude. Again in the mountain native whose external work level more nearly approximated that of the medical student, the stroke work index averaged 135 Gm.M. per minute per square meter, while at the lesser work level this averaged 79 Gm.M. per minute per square meter or about the same as that of the medical student doing much more work.

Calculation of the arteriovenous oxygen difference at rest and during exercise has been made in those instances in which both cardiac output and oxygen consumption were measured. Such values are obviously only an approximation since data for cardiac output and oxygen consumption are based on quite different time intervals. However, they should represent trends. The control data in the mountain native for the calculated arteriovenous oxygen difference averaged 5.72 cc. per 100 cc.; during exercise this increased to 13.86 cc. per 100 cc. At sea level in the medical students for a somewhat greater level of treadmill work the average calculated arteriovenous oxygen difference was 16.86 per 100 cc. The values reported here during exercise are in the same range as those calculated by Asmussen and Nielsen[8] using the dye-dilution technic, and as those reported by Donald and co-workers (9),

in which the arteriovenous oxygen difference was determined directly with the Fick procedure.

Although attempts were made to stress the left ventricle to maximum external effort, whether this was accomplished either in the mountains or at sea level is not known. The data for the last five natives in table 1, group I are suggestive of maximum cardiac effort. Each of these subjects stated at the end of exercise that he was "very tired" or "completely exhausted." In these five individuals at the higher levels of treadmill work (650 to 749 Kg.M. per minute per square meter) the cardiac work index was quite high ranging from 18.06 to 46.43 Kg.M. per minute per square meter and averaging 26.19 Kg.M. per minute per square meter. In those medical students at sea level, who were working at a considerably higher level of treadmill exercise (725 to 986 Kg.M. per minute per square meter) and who were quite tired, cardiac work index ranged from 11.37 to 15.14 Kg.M. per minute per square meter and averaged 12.93 Kg.M. per minute per square meter.

The data obtained on the cardiac response of the partially acclimated subjects at the altitude is presented for completeness. In these the treadmill work load approximated the lower level of work performed by the natives in the altitude and was considerably less than that of the sea level medical students. The values varied from 545 to 602 Kg.M. per minute per square meter (average 572). Compared to the other two groups, the hemoglobin and hematocrit values were intermediate, with the hemoglobin varying from 15.9 to 18.4 Gm. per 100 cc. (average 17.7), and the hematocrit averaging 54.2 with extremes of 50 and 55.9. The heart rate and systemic blood pressure before and during excerise were of the same order of magnitude in all three groups. During exercise the average cardiac index (5.46 L. per minute per square meter), cardiac work index (8.66 Kg.M. per minute per square meter), stroke volume index (34 cc. per minute per square meter), and stroke work index (55 Gm.M. per minute per square meter) were less than the corresponding parameters at sea level and in the fully acclimated high altitude native. However, because of the small number in the group and the presence of upper respiratory infections with fever in some subjects, these results are regarded as equivocal and no interpretation can be made.

Comments

The data suggest that the subject who is native to an altitude of 15,000 feet has a greater cardiac output, cardiac index, cardiac work index, stroke volume, and stroke work index in the standing position than does the sea-level medical student studied at sea level. During treadmill exercise, the external work obtained by the left ventricle was effected by a combination of a large increase in cardiac output and a mild increase in systemic blood pressure. Stroke volume and stroke work index were only mildly elevated since the heart rate was concurrently greatly increased to approximately 180. As a result, the increase in minute work of the left ventricle was largely accomplished by an increase in heart rate and to a lesser extent by an increase in work response with each systole.

The average level reached during exercise for heart rate and blood pressure was approximately the same, but the average values for cardiac index, cardiac work index, stroke volume index, stroke volume, and stroke work index were all higher in the natives at high altitudes than in the medical students at sea level. Since in the students at sea level the rate of performance of external work was considerably greater than in the other group (810 versus 589 Kg.M. per minute per square meter) and since the oxygen consumption during treadmill work was not greatly different in the two groups, the data suggest that for comparable amounts of external work the heart of the native at the altitude responds with a greater effort than the heart of the native sea level dweller at sea level.

An effort was made to elicit the maximum response of cardiac work by the left ventricle. Although it is believed that some of the figures reported here may approximate the maximum effort of which the normal left ventricle is

capable, it is not known whether this was accomplished because of inability to assess properly the degree of exhaustion of the subjects.

Summario in Interlingua

Le responsa que exercitios in le ambulometro provoca in le ventriculo sinistre esseva studiate in nativos del region de Morococha in Peru (altitude 4540 m) e in nativos del region de Lima in Peru (altitude 150 m). Omne le subjectos esseva studiate al altitude al qual illes habeva vivite omne lor vita. In ambe gruppos—illo de Morococha e illo de Lima—le labor externe del ventriculo sinistre esseva effectuate per un combination de un grande augmento del rendimento cardiac e un leve augmento del pression sanguinee in le circulation major. Le volumine per pulso e le labor per pulso esseva solo levemente elevate pro que le rapiditate del corde esseva simultaneemente multo augmentate. Per consequente le augmento de labor del ventriculo sinistre esseva effectuate in grande mesura per le acceleration del corde e in minor mesura per le augmento del labor per pulso. Con comparabile quantitates de labor externe, le ventriculo sinistre de nativos de grande altitudes, examinate a grande altitudes, respondeva per un considerabilemente plus grande effortio que le ventriculo sinistre de nativos de basse altitudes, examinate al nivello del mar. In alicun casos le valores obtenite se approximava possibilemente al maximo del capacitate del ventriculo sinistre.

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References

[1] Rótta, A.: Physiologic condition of the heart in the natives of high altitude. Am. Heart J. **33:** 669, 1947.

[2] —: Right heart catheterization at high altitudes. Symposium Internacional Sobre Biologia de Altitud, Lima, Peru, 1949.

[3] Hurtado, A.: Chronic mountain sickness. J. A. M. A. **120:** 1278, 1942.

[4] —, Merino, C. and Delgado, E.: Influence of anoxemia on the hemopoietic activity. Arch. Int. Med. **75:** 284, 1945.

[5] — and Aste-Salazon, H.: Arterial blood gases and acid-base balance at sea level and at high altitude. J. Appl. Physiol. **1:** 304, 1948.

[6] Nielsen, H. E.: Clinical investigations into the cardiac output of patients with compensated heart disease during rest and during muscular work. Acta med. scandinav. **91:** 223, 1937.

[7] Lilejestrand, G., Lysholm, E. and Nylin, G.: The immediate effects of muscular work on the stroke and heart volume in man. Skandinav. Arch. f. Physiol. **80:** 265, 1938.

[8] Asmussen, E. and Nielsen, M.: The cardiac output in rest and work determined simultaneously by the acetylene and the dye injection methods. Acta physiol. scandinav. **27:** 217, 1953.

[9] Donald, K. W., Bishop, J. M. and Wade, O. L.: A study of minute to minute changes of arteriovenous oxygen content difference, oxygen uptake and cardiac output and rate of achievement of a steady state during exercise in rheumatic heart disease. J. Clin. Invest. **33:** 1146, 1954.

[10] Hickam, J. B. and Cargill, W. H.: Effect of exercise on cardiac output and pulmonary arterial pressure in normal persons and in patients with cardiovascular disease and pulmonary emphysema. J. Clin. Invest. **27:** 10, 1948.

[11] Dexter, L., Whittenberger, J. L., Haynes, F. W., Goodale, W. T., Gorlin, R. and Sawyer, C. G.: Effect of exercise on circulatory dynamics of normal individuals. J. Appl. Physiol. **3:** 439, 1951.

[12] Lewis, B. M., Houssay, H. E. J., Haynes, F. W. and Dexter, L.: The dynamics of both right and left ventricles at rest and during exercise in patients with heart failure. Circulation Research **1:** 312, 1953.

[13] Chapman, D. B. and Fraser, R. S.: Studies on the effect of exercise on cardiovascular function. I. Cardiac output and mean circulation time. Circulation **9:** 57, 1954.

[14] Shadle, O. W., Ferguson, T. B., Gregg, D. E. and Gilford, S. R.: Evaluation of a new

cuvette densitometer for determination of cardiac output. Circulation Research **1:** 200, 1953.

[15] GILFORD, S. R., GREGG, D. E., SHADLE, O. W., FERGUSON, T. B. AND MARZETTA, L. A.: An improved cuvette densitometer for cardiac output determination by the dye-dilution method. The Review of Scientific Instruments **24:** 696, 1953.

[16] THEILEN, E. O., PAUL, M. H. AND GREGG, D. E.: Cardiac output determinations with the cuvette densitometer: Techniques for blood of reduced oxygen saturation. Am. J. Physiol. **179:** 679, 1954.

[17] FERGUSON, T. B., SHADLE, O. W. AND GREGG, D. E.: Effect of blood and saline infusion on ventricular end diastolic pressure, stroke work, stroke volume and cardiac output in the open and closed chest dog. Circulation Research **1:** 62, 1953.

[18] FERGUSON, T. B., GREGG, D. E. AND SHADLE, O. W.: Effect of blood and saline infusion on cardiac performance in normal dogs and dogs with arteriovenous fistulas. Circulation Research **2:** 565, 1954.

QS- and QR-Pattern in Leads V_3 and V_4 in Absence of Myocardial Infarction: Electrocardiographic and Vectorcardiographic Study

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A QS or QR pattern in the absence of myocardial infarction is frequently present in lead V_3 and occasionally in lead V_4. Exploration by means of multiple chest and abdominal unipolar leads and vectorcardiograms revealed that in almost all such cases, the vector of the initial portions of the QRS complex is directed downwards. Accordingly, in the absence of infarction, patients presenting this pattern almost invariably showed an initial R wave in the leads recorded from positions below the standard level of V_3 and V_4. The vast majority of patients with myocardial infarction with a similar QRS pattern showed a Q wave in the lower leads. Consideration of vertical components of cardiac voltages may be helpful in the interpretation of the precordial leads.

THE PRESENCE of a QS pattern or of an abnormally deep and wide Q wave (deeper than 25 per cent of succeeding R wave and wider than 0.04 second) in precordial leads V_3 to V_6 is usually, although not invariably, attributed to myocardial infarction. Occurrence of a QS pattern or of a significant Q wave in leads V_3 and V_4 and on some occasions even in leads V_5 and V_6, in the absence of myocardial infarction, has been demonstrated in cases of left ventricular hypertrophy,[1, 4, 12, 14, 15, 28] hypertrophy or dilatation of the right ventricle[8, 10, 12, 13, 19-22], complete or "incomplete" left bundle branch block,[16, 17, 18, 23-26], right bundle branch block,[23] and displacement of the heart.[15] In his study of electrocardiograms which may be mistaken for myocardial infarction, Myers emphasized the occurrence of these patterns on several occasions. It seems to be justifiable to suspect that in many instances myocardial infarction has been diagnosed incorrectly on the basis of a QS, QR or QRS pattern in the precordial leads. (See fig. 1.) This suspicion is augmented by the fact that there are very few electrocardiographic diagnostic criteria which differentiate a QS or QR deflection of myocardial infarction from an identical deflection caused by other factors.

The present investigation was initiated in the hope of finding a method which might help to differentiate these patterns which are found with myocardial infarction from similar patterns not associated with infarction. At the same time we have attempted to obtain information regarding the factors responsible for the genesis of the QRS patterns which simulate myocardial infarction in the precordial leads.

Two major principles of electrocardiographic diagnosis were applied: (1) exploration of the precordium by means of multiple semidirect unipolar leads; and (2) vectorcardiograms representing the distant indirect leads and picturing the over-all or average electrocardiograms.[11]

Method

The routine, 12-lead electrocardiograms made at the Heart Station of the Philadelphia General Hospital were screened daily during the period from

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August 1953, until March 1954, for patterns displaying a QS complex or a significant Q wave in the standard precordial leads V_3 and V_4. Cases with a QS or QR pattern limited to leads V_1 and V_2 were not included because the occurrence of such patterns in the absence of myocardial infarction is widely known. Cases with a significant Q wave which is deeper than one-fourth of the R wave and wider than 0.04 second in leads V_5 and V_6 were not included because these findings are almost invariably due to infarction. As a result, the selected group included only cases of myocardial infarction in which the QRS changes due to infarction did not extend further to the left than lead V_4 and cases of noninfarction with an absent initial R wave in leads V_3 and V_4 which could have been mistaken for the above infarction pattern. None of the features of the electrocardiogram, other than the QRS complex, were considered in the selection of cases.

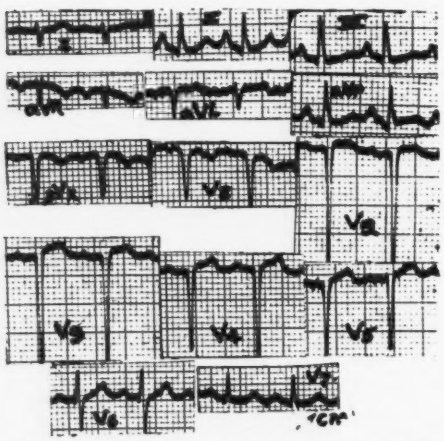

FIG. 1. Electrocardiogram of a 57 year-old Negro man with pulmonary emphysema and a possible Addison's disease 24 hours before death. Myocardial infarction was suspected because of the QS pattern in leads V_2, V_3 and V_4. Autopsy revealed no cardiac abnormalities except slight dilatation of the right ventricle. Heart weight 280 Gm. Thickness of the left ventricle 12 mm.; of the right ventricle, 4 mm.

During the selection of cases for this study, it became obvious that various observers differed in their judgment as to what is a discernible initial R wave. On several occasions a given electrocardiographic QRS complex was designated by some observers as rS while others preferred to call the same complex QS. In order to determine the error which might be due to this factor of difference in interpretation, 15 different complexes with an absent or a very small initial R wave and a deep S or QS wave were presented to 20 experienced cardiologists who were asked whether, in their opinions, the 15 complexes should be designated QS, rS or undeterminable. The results of this inquiry are presented in figure 2. It has become obvious that an R wave smaller than 0.5 mm. can hardly be recognized as such even if the technical recording of the tracing

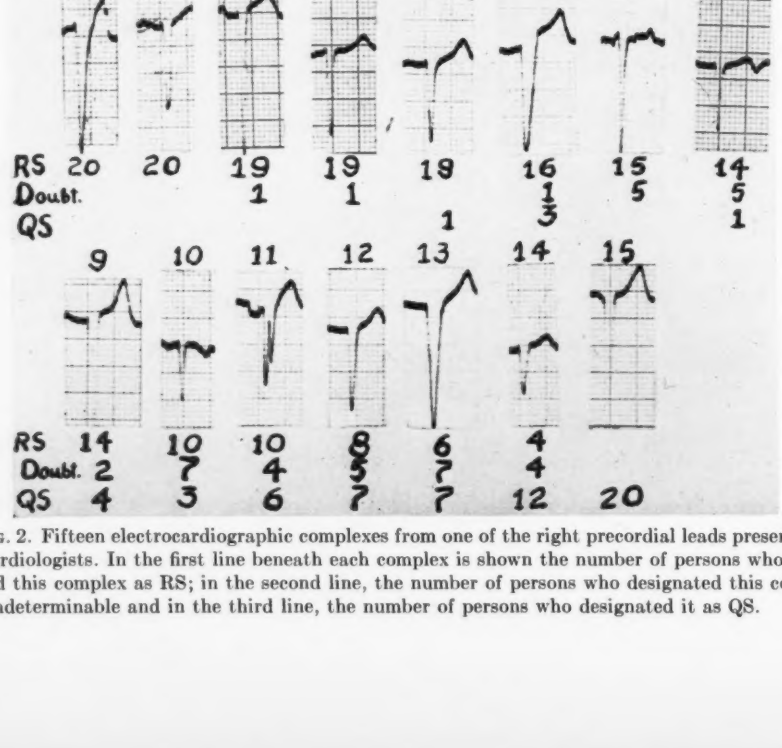

FIG. 2. Fifteen electrocardiographic complexes from one of the right precordial leads presented to 20 cardiologists. In the first line beneath each complex is shown the number of persons who designated this complex as RS; in the second line, the number of persons who designated this complex as undeterminable and in the third line, the number of persons who designated it as QS.

is good. The material selected for this study contains only cases in which all authors of this paper felt that there was no initial R wave in leads V_3 or V_4.

The patients selected for the study were subjected to the following examinations: (1) clinical evaluation, (2) recording of one or two leads synchronously with lead V_3 or V_4, (3) multiple chest and abdominal unipolar electrocardiographic leads, (4) vectorcardiograms and (5) special roentgenologic studies. All these studies were performed on the same day.

(1) The clinical evaluation was based on a careful history and physical examination. The majority of the examined individuals were ward patients whose hospital and out-patient records could be traced back for a varying length of time. From the day on which the patient was selected for study, his course was followed by means of periodic clinical and electrocardiographic examinations. All available autopsy findings were secured.

(2) In order to establish whether the initial negative QRS deflection in leads V_3 and V_4 represented the earliest part of the ventricular depolarization, leads V_3 and/or V_4 were recorded synchronously with lead I, aV_F, and one of the precordial V leads by means of Sanborn-Polyviso direct-writing electrocardiograph.

(3) The electrocardiographic exploration included standard limb and augmented unipolar limb leads, standard precordial leads V_1 through V_6, leads V_E, V_{3R} and V_7 and 26 additional chest and abdominal leads. The additional leads consisted of two groups: leads recorded from the chest at the levels above, and leads recorded from the chest and abdomen below, the standard levels. The high leads were taken from the second and third intercostal spaces at positions V_1 through V_5, from the fourth intercostal space at the position V_3 through V_6 and also from the level of the fifth rib at position V_4. The low leads were taken from the fifth intercostal space at the position V_3, from the ensiform (E) level at the positions V_1 through V_5 and from the epigastric level (ep), which was determined by the mid-point between the ensiform process and the umbilicus, at the positions V_3 through V_5. In some of the later cases, leads from the mid-line at the levels of umbilicus ("O") and between umbilicus and ensiform process ("EO") recommended by Lambert[32] were recorded in addition.

(4) Vectorcardiograms were obtained with Sanborn Vectorcardiograph consisting of the Poly-Viso Recorder Model 64-1300 A, Coupling unit Model 78-100, and the Dumont Cathode Ray Oscillograph Type 304H. The electrode attachment systems were those described by Wilson and his co-workers[11, 39] referred to in this paper as "tetrahedron" and by Grishman and associates[47] referred to in this paper as "cube".

Analysis of the QRS loops was undertaken in the following manner: The initial deflection was taken to be the first four points (0.02 second) emerging from the central blob. The direction of the initial QRS deflection was expressed through reference to the x, y and z axes in both reference systems. The direction of progression of the electron beam was recorded as clockwise or counterclockwise in the horizontal and sagittal planes. The total number of points from the beginning to the end of the QRS loop were counted in each plane. Each plane was then divided into four quadrants and the number of points counted in each quadrant. In addition, in each plane, it was noted in which of the quadrants the major part of the QRS loop area was situated. Irregularities and indentations in the loops were noted and arbitrarily graded from 1 (completely smooth) to 4 (very irregular).

(5) Six-foot chest roentgenograms with the patient in the supine position were obtained with the sites of the standard precordial electrode positions on the chest and abdomen indicated by lead numbers.

Material

Six groups of individuals were studied: Group 1, 24 patients with myocardial infarction; group 2, four patients with possible myocardial infarction; group 3, 25 patients with absent myocardial infarction; and group 4 six patients in whom myocardial infarction was considered unlikely; group 5, 10 patients with left ventricular hypertrophy; and group 6, 10 normal persons without evidence of cardiovascular disease.

Classification of the material in the first four groups was made, without the consideration of the results of special studies, on the basis of the clinical evaluation, follow-up records and autopsy findings, which were available in 10 patients. The group with infarctions included patients with conclusive evidence of myocardial infarction gained from autopsy or a combination of a typical clinical course and serial electrocardiograms. Most of the infarctions had occurred within the preceding 12 months. The group with possible infarctions included patients in whom infarction was suggested by the serial electrocardiograms, but the remaining clinical data were not sufficiently conclusive. The group with absence of infarctions included five patients in whom the diagnosis was established by autopsy and those patients in whom there was no suspicion of infarction either in the history or in the serial electrocardiograms recorded during a period from one to several years prior to the study. The group designated as "infarction unlikely" included similar patients in whom infarction was at no time suspected clinically, but no previous serial tracings were available.

Fifty-nine patients whose data were subjected to final evaluation included 45 males and 14 females. Forty patients were white and 19 were Negroes. The age of the patients ranged from 39 to 84 years, averaging 64.5 years. The distribution of the sex, race and age factors within the two major groups of proven and absent infarction showed no significant differences.

Patients in group 5 were selected at random from the Hospital population. They had proved left ventricular hypertrophy, as determined by x-ray study and an electrocardiographic pattern of left ventricular hypertrophy and "strain". None of them had history of myocardial infarction or chest pain at any time. The group included four males and six females who were 52 to 76 years old with an average age of 62.

Individuals in the group 6 were 25 to 47 years old. Five normal persons had hearts in a vertical anatomical and five in a horizontal anatomical position.

Results

Time of Onset of QRS

The results of the synchronous recording of lead V_3 or V_4 with other leads in all groups of cases can be summarized by a statement that in no case was the initial QRS deflection in leads V_3 or V_4 preceded by an earlier deflection in some other lead. The beginning of the QRS complex in leads V_3 and V_4 coincided usually with the beginning of the QRS complex in other precordial leads (V_1 and V_2) but in more than half of the cases occurred 0.01 to 0.02 second earlier than the QRS onset in the limb leads aV_F or I.

Direction of the Initial QRS Deflection

The differences between the group with myocardial infarctions and the group with possible infarctions on the one hand and the differences between the group with absent infarction and the group in which infarction was unlikely on the other hand were insignificant. It appears to be justifiable, therefore, to discuss only the differences between the group with myocardial infarction and the group with absence of infarction. Following are the more important results:

(a) *Standard Precordial Leads:* In the standard lead V_3, a QS pattern or a significant Q wave was present in 22 out of 24 patients with infarction and in 21 out of 25 patients without infarction. In standard lead V_4, the QS pattern or a significant Q wave was present in three patients without infarction and in nine with infarction. In standard precordial leads V_5 through V_7, the presence of a small Q wave was encountered in 71 per cent of the infarction cases and in only 32 per cent of the noninfarction cases. In standard precordial leads V_{3R}, V_1 and V_2 the groups with infarction and with no infarction showed only insignificant differences. In the majority of the patients in both groups all three right precordial leads showed a QS pattern, but an initial R wave was present in leads V_{3R}, V_1, and in some cases also in V_2 in eight patients with infarction and six without infarction.

In the group of 10 patients with left ventricular hypertrophy, without a QS pattern in leads V_3 and V_4, a QS pattern was present in four cases in lead V_{3R}, and in three cases in leads V_1 and V_2.

(b) *Low Precordial Leads:* In lead V_E an initial R wave was present in 17 per cent of the patients with infarction and in 48 per cent without infarction. The situation was very similar in lead V_{1E} (lead V_1 made at level of ensiform). In lead V_{2E} the difference between the QRS pattern in patients with infarction and without infarction was somewhat larger; the initial R wave was present in only 8 per cent of the patients with infarction and in 56 per cent of the patients without infarction.

The greatest difference between the QRS patterns in the infarction and noninfarction groups was present in lead V_{3E}; the initial R wave was present in 12 per cent of the group with infarction and in 96 per cent of the group without infarction. The pattern in the lead between standard V_3 and V_{3E}, at the level of the fifth intercostal space, was similar to that in lead V_{3E} in the group with infarction, but the presence of the initial R wave in the group without infarction was less frequent than in lead V_{3E}. An initial R wave in leads V_{4E}, V_{5E}, V_{3ep} (lead V_3 made at level of epigastrium) and V_{4ep} in patients without infarction was found as frequently as in lead V_{3E}, but a higher number of patients with infarction showed an initial R wave in leads V_{4E}, V_{5E}, V_{3ep} and V_{4ep} than in lead V_{3E}.

In the group of 10 patients with left ventricular hypertrophy without a QS pattern in lead V_3 and V_4 a QS pattern was present in three patients in lead V_{1E}, in two cases in lead V_E and in one case in lead V_{2E}.

In the group of 10 normal patients, the initial QRS deflection was positive in all low pre-

cordial leads with the exception of a small Q wave in leads V_{4E}, V_{5E}, and leads V_2 through V_5 made at the epigastric level in four cases in which a small Q wave was present in aV_F.

(c) *High Precordial Leads:* Leads from a level one intercostal space higher than the level of the standard precordial leads showed generally great similarity of the initial QRS deflection in both the infarction and the noninfarction groups. In leads V_2 through V_4 made at the second intercostal space, the difference in pattern in the infarction and the noninfarction groups was slightly greater since the initial QRS deflection in these leads was invariably negative in the noninfarction group while it was positive in 36 to 45 per cent of the infarction cases.

In the group of 10 patients with left ventricular hypertrophy without a QS pattern in leads V_3 and V_4, a QS pattern was present in six patients in lead V_1 made at the third and second intercostal spaces, in five cases in lead V_2 taken at the third and second intercostal spaces, in four cases in lead V_3 taken at the third intercostal space and in one case in lead V_4 taken at the second intercostal space.

In the group of five normal subjects with vertical anatomic heart position the initial QRS deflection was positive in precordial leads V_1 through V_5, all made from points above the conventional level. In the group of five normal subjects with horizontal anatomic heart position, a QS or QR deflection was present in one subject in lead V_1 made from the third and second intercostal space and in two subjects in leads V_3 and V_4 made from the level of the second intercostal space.

Vectorcardiograms

Vectorcardiograms were taken on 46 patients of groups 1, 2, 3, and 4. In 43 of these patients, the "tetrahedron" coordination of Wilson (11, 64) was used and in 45 patients the cube modification of Grishman[65] was used. Since the group with proved and possible infarction, on the one hand, and the groups with absent or unlikely infarctions on the other hand showed no significant difference, only differences between the two major groups with proved and absent infarction will be discussed in detail.

(a) *Initial Deflection.* (First 0.02 second of the ventricular depolarization.) The most significant difference between the group with proved and absent infarctions was in the direction of this deflection along the y axis in both coordinate systems. The initial deflection was directed downwards in 90 to 92 per cent of the group without, and in only 36 to 46 per cent of the group with infarction. In the majority of tracings of patients in both groups (64 to 83 per cent) the initial deflection was directed to the left. In the z axis, when the tetrahedron coordinates were used, 75 per cent of the patients with no infarction showed anterior progression, whereas only 36 per cent of the group with infarction showed this progression. With the cube coordinate system there was hardly any difference (57 and 62 per cent).

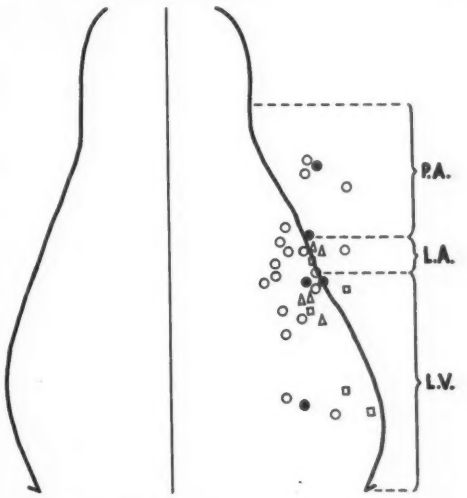

FIG. 3. Position of the electrode in the lead V_3 with relation to cardiac silhouette of the teleroentgenogram is presented in a schematic way. Sectors L.V., L.A. and P.A. correspond to the levels of the left ventricle, left auricle and pulmonary artery on the left side of the heart. The open circles represent cases without infarction, solid circles represent cases with infarction, triangles represent the cases with normal hearts in vertical anatomical position and squares represent cases with normal in horizontal anatomical position.

When analysis was carried out by distribu-

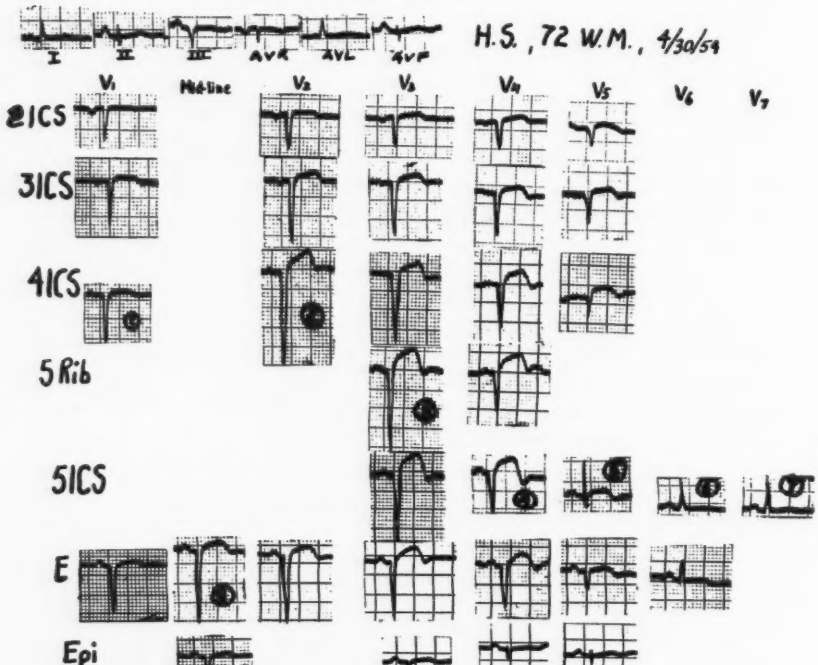

FIG. 4. Electrocardiogram of a 72 year old white man three weeks after myocardial infarction. Typical history of infarction and characteristic serial electrocardiographic changes. Note a QS pattern in leads V_1 through $_4$ and V_{3E}, V_{4E}, V_{3cp}, but an RS pattern in aV_F.

tion in plane quadrants the biggest difference between the two groups in both coordinate systems was found in the sagittal plane. Only 4 to 10 per cent of the group without infarction showed progression of the initial deflection into the posterior superior quadrant of this plane, while 38 to 50 per cent of the patients with infarction showed such progression. The differences in the frontal plane were smaller and in the horizontal plane, negligible. In three dimensional analysis the differences were even smaller. The largest difference between the groups with and without infarction was that the initial deflection of the group with no infarction was directed into the posterior left superior octant in only 4 to 10 per cent, while in the group with infarction the direction into this octant occurred in 29 to 31 per cent.

(b) *Orientation of the entire QRS loop.* Analysis of the characteristics of the loops showed that in both groups the loops were most frequently found in the left posterior and superior octants. The differences in distribution between the infarction and noninfarction groups were insignificant in either coordinate system. Posterior orientation of the loop was encountered more frequently in the tracings recorded with the cube co-ordinate system.

(c) *Direction of rotation of the QRS* $s\hat{E}$. In the tetrahedron system, in the horizontal plane, counterclockwise rotation was encountered slightly more frequently (80 per cent) in the group with no infarction than in the group with infarction (64 per cent), but there was practically no difference between the findings in the two groups in the cube system. In the sagittal plane clockwise rotation was slightly more frequently encountered in the noninfarction group than in the infarction group (43 to 54 per cent) in both systems. The difference between the cube and tetrahedron systems consisted of complete absence of counter-

clockwise rotation in tracings of the noninfarction group taken in the cube system, while it was found in 23 per cent of the tracings in the same group taken with the tetrahedron system. Another difference was a more frequent finding of clockwise rotation in the group without infarction (83 per cent) in the cube system, as compared with the tetrahedron system (65 per cent).

(d) *Irregularities and indentations of the QRS loop.* In both systems perfectly smooth loops were observed somewhat more frequently in the group without myocardial infarction (26 to 40 per cent), than in patients with infarction (14 to 15 per cent). Marked irregularities were no more common in the group with infarction (22 to 23 per cent) than in the group with no infarction (13 to 30 per cent) in both systems. Nor was there any significant difference in the distribution of moderate irregularities between the two groups.

Comparison of the Findings in Low Precordial Leads with Findings in Lead aV_F of the Electrocardiogram

In view of the finding pointing to the conclusion that precordial leads V_3 and V_4 recorded at the ensiform and epigastric levels showed very significant differences in the direction of the initial QRS deflection between the group with infarction and the group with no infarction, it appeared necessary to compare the findings in these leads with those in lead aV_F. Lead aV_F is the only standard unipolar lead recorded routinely in which the electrode is placed below the level of the standard precordial leads.

In our patients without infarction, the initial QRS deflection in aV_F was positive in 24 out of 25 cases and coincided in 96 per cent with the initial QRS deflection of lead V_{3ep} and in 92 per cent with the initial QRS deflection of lead V_{3E}.

Out of the 21 cases of infarction with an initial negative QRS deflection in lead V_{3E} only 10 cases showed an initial negative QRS deflection in aV_F. In the remaining 11 cases, in which the initial QRS deflection was positive in aV_F, two cases showed an initial negative QRS deflection in all examined low precordial leads, five cases showed an initial positive QRS deflection only in leads V_{4ep} (fig. 4), four cases in leads V_{4ep} and V_{3ep}. Leads from the umbilical and epigastric levels in the midline (leads V_O and V_{EO} of Lambert) were recorded

TABLE 1.—*Subdivision of 25 Cases Without Infarction*
Sex: M.—18; F.—7. Race: W.—16; C.—9.
Age Distribution 39–84, Av. 65

Condition	No. of Cases
HHD	8
HHD & severe kyphoscol	1
HHD & bullous emphys	1
Cor pulmon. emphys	1
Cor pulmon. pulm. fibrosis	1
Cor pulmon. pulm. tb	2
Cor pulmon. sarcoid	1
Aortic sten. & insuff	4
Aortic & mitral dis	1
IV sept. defect	1
Senile degener. HD	1
Thyrotoxic HD	1
Emphysema, no heart disease	1
No heart & lung dis	1
Total	25
Anatomic Diagnosis	**No. of Cases**
LVH	13
LVH?	3
LVH & RVH	3
RVH	1
Diffuse cardiomeg	1
Normal heart	4
Total	25
ECG Pattern	**No. of Cases**
LBBB	3
"LV strain"*	11
LVH without T inversion*	3
RVH	1
Normal with deep S2-3	3
Normal	3
RBBB	1
Total	25

* These cases had an absent Q wave in V5 through 7, but QRS duration was less than 0.10 sec.

Abbreviations: HHD—hypertensive heart disease. LVH—left ventricular hypertrophy. RVH—right ventricular hypertrophy. LBBB and RBBB—left and right bundle branch block.

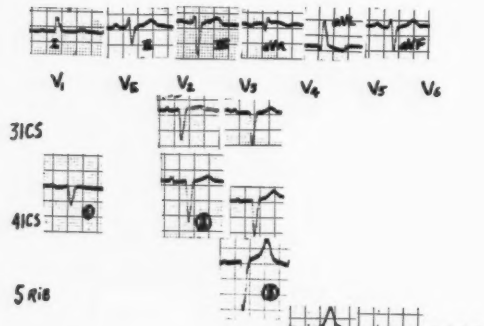

FIG. 5. Electrocardiogram of a debilitated 80 year-old white man with a staphylococcus septicemia. Death 11 days after admission. Autopsy revealed severe dilatation of both ventricles. Heart weight 520 Gm. Circular interventricular septum with an area of erosion at the edge and soft friable vegetations extending to the tricuspid valve. No evidence of past or recent myocardial infarction. Note a QS pattern in V_3 and an initial R wave in V_{3E} and V_{3ep}.

only in four patients with myocardial infarction. In one of these cases the initial QRS deflection was negative in leads V_{3E}, V_{3ep} and V_{4E}, but positive in leads V_O and V_{EO}.

Relation of Electrode Position to Anatomic Position of the Heart as Shown by X-ray Examination.

Chest roentgenograms with electrode positions marked on chest surfaces were available in 18 patients with no infarction, in five patients with myocardial infarction, in five normal subjects with vertical and in five normal subjects with anatomically horizontal hearts. The positions of the electrodes were evaluated with regard to their projection on the cardiac shadow.

Lead V_1: The electrode was located over the great vessels in the majority of cases. It did not overlay the ventricles in a single case.

Lead V_2: The electrode was located over the ventricle only in one-half of the normal patients and in one-sixth of the patients without infarction.

Lead V_3: Figure 3 shows in a semischematic way the relation of the electrode to the cardiac silhouette in all cases.

Lead V_4: The electrode was located over the ventricle (presumably the left) or the area outside of the heart shadow at the level of the ventricles in all examined cases in all groups. In the normal subjects with horizontal hearts the electrode was close to the apex, in the other three groups the electrode positions varied from a site over the apex to a site over the upper border of the ventricle.

Leads V_5 and V_6: In all cases of all groups the electrode was located outside of the heart shadow at the level of the ventricles.

Analysis of Individual Cases

Twenty-five patients with no infarction represented a variety of clinical and anatomic conditions and electrocardiographic patterns which are summarized in table 1. A representative case is illustrated in figure 5.

In one of the patients without infarction, it was noted that the QS deflection in V_3 gave way to an rS deflection during deep expiration. In another case without infarction a QS pattern in lead V_3 changed into rS after removal of 500 cc. of right-sided pleural effusion.

DISCUSSION

The number of tracings with an absent R wave in lead V_3 in patients without infarction was surprisingly high. The exact number of screened electrocardiograms is unknown, but it can be estimated at 5000 to 6000 tracings, which would give an incidence of the discussed pattern of about 0.5 per cent of all electrocardiographic tracings.* Accordingly a QS or QR pattern in lead V_3 in the absence of myocardial infarction is not very uncommon. This is in agreement with the impression gained from the review of literature.

The incidence of a QS or QR pattern in lead V_4, in the absence of myocardial infarction,

* This number of electrocardiograms does not represent the number of patients since several tracings might have been recorded in the same individual.

was much less frequent and did not exceed 0.015 per cent. No instances of a QS or QR pattern in lead V_5, in the absence of myocardial infarction, were encountered in this study, although proven cases are on record.[10]

The most important result of this study appears to be the finding of a method which enables one to determine, in a great majority of cases, whether or not a QS or QR pattern in leads V_3 and V_4 is due to infarction. The method consists in the recording of additional electrocardiographic leads at the ensiform and epigastric level below the positions on the chest at which V_3 and V_4 are conventionally recorded. For practical purposes recording of only one additional unipolar precordial lead, V_{3E} (lead V_3 recorded at the level of the ensiform), is probably sufficient.

In all of the patients without infarction, the transition between the initial negative and the initial positive QRS deflection in the leads placed along the vertical axis on the anterior body surface, occurred below the level at which the conventional leads V_3 and V_4 are recorded. This implies that, in all cases without infarction with an absent R wave in leads V_3 and/or V_4, the initial QRS vector was directed downward, and the anatomical point of the origin of this vector was situated below the level of the standard leads V_3 and V_4. This was supported by the vectorcardiograms which showed an initial downward spread of excitation in 90 to 92 per cent of the QRS loops of the cases without infarction.

Most of our cases with infarction showed a Q wave in the lead V_{3E}. If one assumes that the Q wave in the precordial leads appears when the electrode faces the infarcted area, this finding indicates that the infarction in the above mentioned cases probably affects the inferior portion of the anterior heart wall. Among the 24 cases of infarction there was only one unequivocal case with a QS pattern in leads V_3 and V_4 in which an R wave was present in the leads recorded from positions below the conventional leads.

An electrocardiographic pattern of myocardial infarction in which QRS changes are present in standard precordial leads V_1 through V_4, and leads III and aV_F has been frequently encountered in the present study. This pattern has been described on numerous occasions:[27, 7, 31, 40, 33, 29, 36, 37, 42, 8, 1, 41, 32] (these references are in chronological order) and designated as anteroseptal,[30, 7] extensive infarction of septum involving the anterior and posterior wall,[29] anteroposterior,[1, 42, 7] and posteroinferior infarction.[8]

In two of our cases with such an electrocardiographic pattern, which came to autopsy, there was an occlusion of the descending branch of the left coronary artery with involvement of the anterior wall, inferior half of the septum in both and part of the posterior wall in addition in the other case.

Value of High Precordial Leads

Our study indicates that chest leads recorded from the levels above the standard precordial positions were of little value in differentiation between infarction and noninfarction patterns. The occurrence in normal subjects of a QS pattern in high right precordial leads[1, 8, 48] was confirmed by us. In normal persons with hearts in a horizontal position, we also found a QS pattern in leads V_3 and V_4 taken at the level of the second intercostal space.

High precordial leads have been utilized for diagnosis of myocardial infarction.[30, 43-45, 1, 5] Our study leads to the conclusion that in the majority of instances a Q wave in high precordial leads does not necessarily indicate myocardial infarction. In contrast to cases without infarction, a significant percentage of our patients with infarction (28 to 40 per cent) showed the presence of an initial R wave in leads V_1 and V_6 made one to two intercostal spaces above the standard level.

Absence of an Initial R Wave in Some Precordial Leads in the Presence of an R Wave in Leads made from Positions to the Right of these Leads

Such patterns, as well as progressive diminution of R from right to left precordial positions, have been considered to be suggestive of anterior or anteroseptal myocardial infarction.[2, 18, 33] It has been noted, however, that in cases of right ventricular dilatation without myocardial infarction, an R wave may be present in lead V_1 and either diminish in size or disappear in transitional leads toward the left precor-

dium.[18] In our cases with QS or QR pattern in leads V_3 and V_4, an initial R wave was present in leads V_{3R}, V_1 and occasionally in V_2 in one-third of the patients with infarction and in almost one-fourth of the cases without infarction. This indicates clearly that this pattern is not specific for myocardial infarction. One or two of our cases without infarction, with the described pattern, might have had dilatation of the right ventricle but the majority had clinically and electrocardiographically an uncomplicated left ventricular hypertrophy.

Direction of the Initial QRS Deflection in Absence of Infarction

(a) *Transverse Axis:* In 14 of our cases without infarction, the initial deflection of QRS was caused by forces directed from right to left. Only three of these cases had a QRS duration exceeding 0.12 second, while in the remaining cases there was a left ventricular "strain" pattern with a QRS duration of 0.08 to 0.10 second.* In the remaining 11 cases of absent myocardial infarction, the initial QRS deflection was caused by forces directed from left to right, though the transition between the initial positive deflection on the right side and the initial negative deflection on the left side was not found in the standard precordial leads, but in the leads made from a site below the level of the standard precordial leads.

(b) *Vertical Axis:* In the cases of left ventricular hypertrophy selected at random, the initial deflection of QRS was caused by forces directed downward in 7 out of 10 cases. In 25 cases without infarction with an initial negative deflection of QRS in V_3 and V_4, the initial deflection of QRS was caused by forces directed downward in all cases as indicated by the results of the exploration and in 92 per cent as indicated by vectorcardiograms. The majority of these cases consisted of cases of left ventricular hypertrophy. Whether the development of left ventricular hypertrophy causes the vector of the initial deflection of QRS to assume a more downward direction in all cases remains to be proven. However, such a shift appears to be probable because of our observation of a progressive diminution of the size of the initial R wave in the right precordial leads in several cases in which serial tracings over a period of many years were observed.

Causes of Negative Initial Deflection of QRS in the Standard Precordial Leads in the Absence of Myocardial Infarction or Other Conditions in Which a Part of the Myocardium is Dead or Electrically Inactive

These may be the following: (1) atypical spread of excitation, e.g., the precordial electrode faces the same portions of the heart as in normal persons, but the electrical forces have changed their direction; (2) normal ventricular excitation but an altered position of the precordial electrode, e.g., the electrode faces such portion of the heart in which the initial QRS deflection is normally negative.

(1) *Atypical Spread of Excitation.* A negative initial deflection of QRS in the precordial leads can be due either to the presence of an initial negative deflection instead of a positive one or to an absence of the normal positive deflection. The latter concept has been advanced in order to explain a QRS pattern in the transitional leads. It has been postulated that the initial deflection of QRS is nearly perpendicular to the axis of the exploring electrode and thus not recorded at all.[4,10,1,5] Such a situation has been attributed to the depolarization of both sides of the septum at the same time and thus to cancellation of opposite vectors derived from a septal activation.[10] If this were true, the initial deflection of QRS in the precordial leads from the transitional leads displaying QS pattern would be isoelectric. The results obtained in this study show that the beginning of QRS complex occurred at the same time in the leads with a QS or QR pattern as in other synchronously recorded precordial leads. Accordingly, the concept of an initial isoelectric deflection of QRS cannot be used to explain an initial negative QRS deflection in our cases.

The initial deflection of QRS in the right and in the transitional precordial leads may be negative if the spread of excitation is directed

* Whether these cases have to be designated as incomplete left bundle branch block or not appears to be a debatable subject which is beyond the scope of this paper.

from right to left which presumably takes place in high left bundle branch block. Our non-infarction cases with an initial negative QRS deflection in leads V_3 and V_4 included only 14 cases in which the initial deflection of QRS was considered to be caused by forces directed from right to left while in the remaining 11, the initial deflection of QRS was caused by forces directed from left to right. Therefore, it appears to be doubtful whether one can interpret an electrocardiographic deflection in the unipolar chest leads without taking into consideration the vertical components of the cardiac voltages. Our findings indicate that in all cases without infarction the initial QRS vector was directed inferiorly. This explains the negative initial deflection of QRS in all leads recorded from sites above the anatomical point of the origin of this vector and the positive initial deflection of QRS in all leads made from sites below this point, regardless of whether the downward spread has a right-to-left direction, a left-to-right direction or is vertical. This explanation holds if the initial QRS vector in all such instances is directed anteriorly.

For the sake of completeness, one has to mention some other concepts concerning the same problem. An initial Q wave in right precordial leads has been attributed to congenital variation in the distribution of conduction fibers.[6] An absent R wave in precordial leads in certain cases of right and left ventricular hypertrophy has been attributed to a decreased density of the junctions between Purkinje fibers and ordinary muscle as a result of dilatation of the affected chamber.[30] It has been postulated recently that absence of an initial R wave in right precordial leads in cases of left ventricular hypertrophy is due to a posterior spread of the initial deflection of QRS as a result of stretching and bowing of the inflow tract of the left ventricle.[34]

(2) *Change in position of the electrode in relation to the heart.* The negative initial deflection of QRS in the standard precordial leads cannot be satisfactorily explained without taking into consideration this second factor. This can theoretically occur either because of a change of heart position with relation to the electrode or because of a change of the electrode position with relation to the heart. The last factor may play some role in certain chest deformities in which the upper ribs anteriorly are closer together than normally, thus making the intercostal spaces narrower and the position of the standard electrodes higher than normal. In one of our cases such a situation was believed to be present. The factor of change of the position of the heart with relation to the electrodes appears to be of more practical importance. Pardee has demonstrated on x-ray films of six individuals that the electrode in leads V_2 and V_3 in the sixth intercostal space lies over the ventricles more frequently than in standard leads V_2 and V_3 which overlay supraventricular structures.[35] Figure 10 of reference 19 shows the x-ray film of a patient with right ventricular hypertrophy in whom the position of the V_3 electrode is close to the pulmonary artery segment. On the other hand, fairly numerous postmortem determinations in which the electrode position was correlated with the heart position have demonstrated the position of the V_3 electrode to be near the interventricular septum in persons with normal hearts, to the right of the septum in patients with left ventricular hypertrophy, and to the left of the septum in subjects with right ventricular hypertrophy.[13] The horizontal level of the electrode in the last study was not mentioned, but the illustrated variations of position appear to be of considerable magnitude. Six teleroentgenograms in normal students were made by Kossman and Johnston and in one illustrated case electrode V_3 overlies the lower part of the left ventricle.[46]

The results of our x-ray study support the opinion of Pardee[35] that in order to have the electrode closer to the ventricles one has to record leads V_2 and V_3 at lower levels than the present standard level used for these leads. It is difficult to establish with any degree of accuracy whether the absence of an initial R wave in our cases without infarction was due in an appreciable number of cases to a high electrode position with relation to the heart. The comparison with the small control group of normal persons, which show a similar electrode position in relation to the heart, suggests that this is not a crucial factor. It appears to us that the

low position of the anatomic point of the origin of the initial QRS vector was of greater importance as a factor producing the QS deflections in the precordial leads than the low position of the diaphragm or other changes of the anatomic position of the whole heart.

Correlation Between Vectorcardiographic Loops and Scalar Electrocardiographic Patterns Obtained With the Chest Leads

In view of the many theoretical and practical difficulties of vectorcardiography, it is not surprising that the vectorcardiogram did not differentiate between patients with and those without myocardial infarction. The initial deflection of the QRS complex corresponds to the first 0.02 second or more of the QRS sÊ-loop. In many of the photographs, the white spot made by the P and T waves is sufficiently large to cover a portion of the QRS loop. This is often a significant factor as proved by a count of the time dots in the same loop in different planes. The QRS duration varied at times as much as 100 per cent in the three planes. It is, therefore, frequently impossible to be sure that the time dots interpreted to be the recording of the potential of depolarization in the first 0.02 second are actually recorded at that time. In general, the vectorcardiogram correlated poorly with leads V_3 and V_4, frequently showing an anterior direction of the initial QRS vector when no initial R waves were recorded in these scalar leads. Although this anterior direction of the initial QRS vector occurred much more frequently in the absence of infarction, the correlation with the clinical findings was not sufficiently good to be of differential diagnostic importance. On the other hand, correlation of vector loops with high and low precordial leads was very much better. Inferior direction of the initial QRS vector was usually seen in patients with initial R waves in leads made from sites below the standard positions, and superior direction of the initial QRS vector in patients with initial R waves in high chest leads. This better correlation of the y axis of the vector and scalar electrocardiogram may be due to the lesser skewing of this axis by cardiac eccentricity.[38] None of the other frequently mentioned signs of infarction (irregularity of the loop, change in rotation of the QRS sÊ) significantly differentiated between the subjects of the infarction and noninfarction groups.

The differences between the loops inscribed by the cube and the tetrahedron coordinate systems were often considerable. Nevertheless, there was no very significant difference between them in the ability to differentiate patients with from patients without infarction.

Summary

(1) A QS pattern or a significant Q wave in the lead V_3 was found in 25 patients in whom myocardial infarction was considered to be absent (in five patients the findings were proved at autopsy) and in six patients in whom myocardial infarction was considered to be unlikely. A similar QRS pattern in lead V_4 was found in only three of these patients. The majority of the patients in this group had left ventricular hypertrophy.

(2) The initial QRS deflections of the electrocardiogram and the vectorcardiogram of the group of patients with a QS or QR pattern in leads V_3 and V_4 who had no infarction and of a group of patients with infarction who had a similar QRS pattern were compared. The electrocardiogram included 26 additional chest and abdominal unipolar leads. The vectorcardiograms were recorded by means of the tetrahedron and cube reference systems.

(3) The differences between the groups of patients with and without infarction with regard to the direction of the initial QRS deflection and the features of the vectorcardiographic QRS sÊ loop are discussed. The most significant differences between the group with infarction and the group without infarction were found in the low chest leads V_3 and V_4 recorded at the ensiform and the epigastric levels. Lead V_3 made at level of ensiform (V_{3E}) showed the greatest difference: an initial R wave was present in 24 out of 25 cases without infarction and in only 3 out of 24 cases with infarction. Thus, the direction of the initial QRS deflection in lead V_{3E} differentiated in 84 per cent patients with infarction from those without infarction

even when the standard lead V_3 showed the same QRS pattern in both groups of patients.

(4) In chest leads made from sites above the standard level, the QRS pattern was not significantly different in the group with and the group without infarction, although the presence of an initial R wave in the high leads occurred more commonly in patients with infarction.

(5) No vectorcardiographic feature differentiated the infarction and noninfarction groups in a significant number of cases. The greatest difference between the two groups concerned the initial 0.02 second of the QRS loop, which was directed inferiorly in 90 to 92 per cent of the patients without infarction and in only 36 to 46 per cent of those with infarction.

(6) Fifty per cent of patients with infarction who had a Q wave in the low chest leads made at the ensiform or epigastric levels showed an initial R wave in lead aV_F.

(7) The teleroentgenograms recorded in the supine position with electrode positions marked on the chest revealed that the electrode for lead V_3 faced the level of the ventricles in only 5 out of 18 patients without infarction who showed a QS pattern in leads V_3 and V_4. In the remaining 13 cases, the electrode (V_3) faced higher levels of the heart. However, the position of the electrodes with relation to the cardiac silhouette was fairly similar in a control group of five patients with infarction and five normal persons with a vertical anatomical heart position. In a group of five normal subjects with horizontal anatomical heart position, the electrodes faced generally lower portions of the heart shadow than in the other groups.

(8) The causes of an initial negative QRS deflection in the absence of myocardial infarction are discussed. The inferior direction of the initial QRS vector and the low location of the point of origin of this vector rather than the low position of the whole heart appeared to be responsible for the absent initial R wave in leads V_3 and V_4 in our patients without infarction.

(9) The consideration of the vertical components of the cardiac voltages may be useful in explanation of the electrocardiographic patterns in the unipolar chest leads.

Summario in Interlingua

Un configuration QS o QR in le absentia de infarcimento myocardial es frequentemente presente in le derivation V_3 e a vices in le derivation V_4. Un exploration per medio de multiple derivationes unipolar e vectocardiogrammas del thorace e abdomine revelava que in quasi omne tal casos le vector del portion initial del complexo QRS exhibi un direction in basso. Consequentemente, in le absentia de infarcimento, patientes monstrante iste configuration exhibiva quasi invariabilemente un unda R initial in le derivationes obtenite ab positiones infra le nivello standard pro V_3 e V_4. Le grande majoritate del casos de infarcimento myocardial con simile configurationes QRS monstrava un unda Q in le derivationes inferior. Le consideration de componentes vertical de voltages cardiac es possibilemente de adjuta in le interpretation del derivationes precordial.

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REFERENCES

[1] Barker, J. M.: The Unipolar Electrocardiogram, New York, Appleton-Century, 1952.

[2] Myers, G. B., Klein, H. A. and Hiratzka, T.: Normal variations in multiple precordial leads. Am. Heart J. **34:** 785, 1947.

[3] Sokolow, M. and Friedlander, R. D.: The normal unipolar precordial and limb lead electrocardiogram. Am. Heart J. **38:** 674, 1949.

[4] Myers, G. B.: QRS-T patterns in multiple precordial leads that may be mistaken for myocardial infarction. I. Left ventricular hypertrophy and dilatation. Circulation **1:** 844, 1950.

[5] Gazes, P.: Normal unipolar variants with special reference to the Q and T waves. Am. Heart J. **40:** 30, 1950.

[6] Dressler, W., Roesler, H and Schwager, A.: The electrocardiographic signs of myocardial infarction in the presence of bundle branch block. Am. Heart J. **39:** 544, 1950.

[7] Kossmann, C. E. and De La Chappelle, C.: The precordial electrocardiogram in myocardial infarction. Am. Heart J. **15:** 700, 1938.

[8] Lepeschkin, E.: Modern Electrocardiography. Baltimore, Williams & Wilkins, 1951, vol. 1.

[9] Vaquero, M., Limon Lason, R. and Limon Lason, A.: Electrocardiogramma normal, estudio de 500 casos en derivaciones standard y unipolares. Arch. Inst. cardiol. Mexico **17:** 155, 1947.

[10] Myers, G. B.: QRS-T patterns in multiple precordial leads that may be mistaken for myocardial infarction. II. Right ventricular hypertrophy and dilatation. Circulation **1:** 860, 1950.

[11] Wilson, F. N., Johnston, F. D. and Kossmann, C. E.: The substitution of a tetrahedron for the Einthoven triangle. Am. Heart J. **33:** 594, 1947.

[12] Myers, G. B., Klein, H. A. and Stofer, B. E.: The electrocardiographic diagnosis of right ventricular hypertrophy. Am. Heart J. **35:** 1, 1948.

[13] Rosenburg, M. J. and Agress, C. M.: Position of precordial leads. Am. Heart J. **38:** 593, 1949.

[14] Benchimol, A. B. and Schlesinger, P.: Electrocardiographic changes in a case of left ventricular and septal hypertrophy resembling anterior myocardial infarction. Circulation **1:** 970, 1950.

[15] Cutts, F. B., Clagett, H. A. and Fulton, F. T.: Smallness or absence of initial positive deflections in the precordial electrocardiogram and cardiac infarction. Arch Int. Med. **67:** 509, 1941.

[16] Jones, A. M. and Feil, H.: The effect of posture upon axis deviation in human bundle branch block. Am. Heart J. **36:** 739, 1948.

[17] Lapin, A. W. and Sprague, H. B.: Respiratory movement as a factor in the production of Q waves in lead 1 and in unipolar leads from the left precordium in human left bundle branch block. Am. Heart J. **35:** 962, 1948.

[18] Myers, G. B., Klein, H. A. and Stofer, B. E.: Correlation of electrocardiographic and pathologic findings in antero-septal infarction. Am. Heart J. **36:** 535, 1948.

[19] Kossmann, C. E., Berger, A. R., Brumlik, J. and Briller, S. A.: An analysis of causes of right axis deviation based partly on endocardial potentials of the hypertrophied right ventricle. Am. Heart J. **35:** 309, 1948.

[20] Zuckermann, R., Cabrera, E., Fishleder, B. L. and Sodi-Pallares, D.: Electrocardiogram in chronic cor pulmonale. Am. Heart J. **35:** 421, 1948.

[21] Johnson, J. B., Ferrer, I., West, J. R. and Cournand, A.: The relation between electrocardiographic evidence of right ventricular hypertrophy and pulmonary arterial pressure in patients with chronic pulmonary disease. Circulation **1:** 536, 1950.

[22] Schlesinger, P., Benchimol, A. B. and Cotrim, M. R.: Intracavity and esophageal potentials in right ventricular hypertrophy. Am. Heart J. **37:** 110, 1949.

[23] Myers, G. B.: QRS-T patterns in multiple precordial leads that may be mistaken for myocardial infarction. III. Bundle branch block. Circulation **2:** 60, 1950.

[24] Rosenbaum, M. B.: Semiologia de la onda Q VI. Ondas Q y QS en las derivaciones precordiales derechas. Prensa Med. Argent. **40:** 33, 1953.

[25] Sodi-Pallares, D., Estandia, A., Soberon, J. and Rodriguez, I.: The left intraventricular potential of the human heart. Am. Heart J. **40:** 655, 1950.

[26] Dressler, W., Roesler, H. and Schwager, A.: The electrocardiographic signs of myocardial infarction in presence of bundle branch block. I. Myocardial infarction with left bundle branch block. Am. Heart J. **39:** 217, 1950.

[27] Wolferth, C. C. and Wood, F. C.: Acute cardiac infarction involving anterior and posterior surfaces of left ventricle. Arch. Int. Med. **56:** 77, 1935.

[28] Kilaidonis, P., Tilmant, J., Gouffalt, J., Deschamps, H. and Carouso, G.: Contribution a l'etude de l'hypertrophie ventriculaire gauche. Arch. mal coeur **42:** 700, 1949.

[29] Roesler, H. and Dressler, W.: An electrocardiographic pattern of infarction of the interventricular septum, extending from the anterior to the posterior aspect of the heart. Am. Heart J. **34:** 817, 1947.

[30] Wilson, F. N., Rosenbaum, F. F. and Johnston, F. D.: Interpretation of the ventricular complex of the electrocardiogram. Advances Int. Med. **2:** 1, 1947.

[31] Hurwitz, M., Langendorf, R. and Katz, L. N.: The Diagnostic QRS Patterns in Myocardial Infarction. Ann. Int. Med. **19:** 924, 1943.

[32] Lambert, J.: Value of additional thoracic and abdominal unipolar leads for diagnosis of the location and extension of myocardial infarctions. Am. Heart J. **47:** 40, 1954.

[33] Wilson, F. N., Johnston, F. D., Rosenbaum, F. F., Erlanger, H., Kossmann, C. E., Hecht, H., Cotrim, N., Menezes de Olivera, R., Scarsi, R. and Barker, P. S.: The precordial electrocardiogram. Am. Heart J. **27:** 19, 1944.

[34] Grant, R. P.: The relationship between the anatomic position of the heart and the electrocardiogram. Circulation **7:** 890, 1953.

[35] Pardee, H. E. B.: Clinical Aspects of the Electrocardiogram. New York, Paul B. Hoeber, 1941.

[36] Kisch, B. and Richman, B. P.: The Q wave in the chest leads. Exper. Med. & Surg. **5:** 331 1947.

[37] Littman, D.: Infarction of the interventricular septum. New England J. Med. **241:** 89, 1949.

[8] FRANK, E.: A direct experimental study of three systems of spatial vectorcardiography. Circulation **10:** 101, 1954.

[9] ABILDSKOV, J. A., BURCH, G. E. AND CRONVICH, J. A.: The validity of the equilateral tetrahedron as a spatial reference system. Circulation **2:** 122, 1950.

[10] BAER, S AND FRANKEL, H.: Studies in acute myocardial infarction. Arch. Int. Med. **73:** 286, 1944.

[11] RODRIGUEZ, M.[1] I., ANSELMI, A. AND SODI-PALLARES, D. P.: The electrocardiographic diagnosis of septal infarction. Am. Heart J. **45:** 525, 1953.

[12] MYERS, G. B., KLEIN, H. A. AND HIRATZKA, T.: III. Correlation of electrocardiographic and pathologic findings in antero-posterior infarction. Am. Heart J. **37:** 205, 1949.

[43] WILSON, F. N., JOHNSTON, F. D., ROSENBAUM, F. F. AND BARKER, P. S.: On Einthoven's triangle, the theory of unipolar electrocardiographic leads and the interpretation of the precordial electrocardiogram. Am. Heart J. **32:** 277, 1946.

[44] ROSENBAUM, F. F., WILSON, F. N. AND JOHNSTON, F. D.: The precordial electrocardiogram in high lateral myocardial infarction. Am. Heart J. **32:** 135, 1946.

[45] LEVY, L., II. AND HYMAN, A. L.: Difficulties in the electrocardiographic diagnosis of myocardial infarction. Am. Heart J. **39:** 243, 1950.

[46] KOSSMANN, C. E. AND JOHNSTON, F. D.: The precordial electrocardiogram. Am. Heart J. **10**; 925, 1935.

[47] GRISHMAN, A., BORUN, E. R. AND JAFFE, H. L.: Spatial vectorcardiography: technique for the simultaneous recording of the frontal, sagittal and horizontal projections. I. Am. Heart J. **41:** 483, 1951.

[48] SOULIE, P., MICHEL, J. AND BAYGIN, R.: Les derivations precordiales hautes chez le sujet normal et les coronariens. Arch. mal. coeur **41:** 289, 1948.

A New Quantitative Basis for Electrocardiographic Theory: The Normal QRS Complex

By Ernest Frank, Ph.D., Calvin F. Kay, M.D., George E. Seiden, M.D. and Robert A. Keisman, M.D.

A theory of electrocardiography based on a fixed-location, eccentric-dipole representation of ventricular depolarization and a homogeneous, resistive, linear medium in the shape of the human torso yields quantitative predictions of instantaneous amplitude and shape of QRS body surface potentials on one normal human subject to an accuracy of approximately ±15 per cent for electrodes dispersed over the entire torso.

ALTHOUGH ELECTROCARDIOGRAPHIC THEORY has been in a formative state since the time of Einthoven, progress has been slow for a variety of reasons. First, the complexity of the electrical system comprised of heart and body and its variability from one human to another have tended to obscure basic characteristics common to all subjects. Second, attention has too often been concentrated, and understandably so, on diseased hearts rather than probing into basic aspects of normal cases. Third, ability to recognize heart disorders, based on purely empiric electrocardiographic observations, which has indeed been fortunate, has at the same time exerted a negative influence on development of an accurate theory. Fourth, background and training of research electrocardiographers has often been inadequate in mathematics, physics, electrical theory and measurement which are fields of extreme relevance to electrocardiography. The result has been, in many instances, noncontributing research effort, acceptance of erroneous concepts and formation of opposing schools of thought.

These formidable difficulties are gradually being overcome by an increasing number of research teams with members trained in complementary disciplines seeking an accurate quantitative theory. As in all science, establishment of such a theory gives insight into complexities, provides a basis for penetrating research and leads to growth of knowledge outstripping by far that which could take place solely on an empiric basis. For the theory of electrocardiography proposed here, quantitative experimental methods and resulting data provide a basis for ascertaining its validity. This theory is shown to predict results of extensive measurements of the QRS complex on one normal male subject to an accuracy of approximately ±15 per cent. It is the first complete three-dimensional theory of electrocardiography which weds precordial and limb potentials in a unified manner, which has been tested in an exacting and comprehensive manner, and which displays an accuracy comparable to experimental errors inherent in measurements of the human system. It is presented as a foundation upon which to continue quantitative developments in this field.

The Theory

The complete unified theory for the normal QRS complex is based on the following assumptions: (1) It is assumed that ventricular depolarization may be represented at each instant of time by an equivalent dipole whose strength and orientation are variable with the individual but whose location is fixed at a single (but generally different) anatomic point for each individual. (2) It is assumed that the medium in which heart currents are produced is homogeneous, resistive and linear for all individuals, but has boundaries the same as the individual subject. These assumptions specify completely an electrical system in which a unique and determinable relationship exists between poten-

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tials on the boundary surface and the internal dipole. A discussion of the experimental and theoretical bases for each of the above assumptions follows.

Ventricular depolarization. Despite substantial and continuing effort, the mechanism, sequence and factors influencing ventricular depolarization are not completely understood. This does not present a barrier to analysis of body surface potentials because it is fundamentally impossible to obtain information concerning the detailed activity of the internal heart generator *exclusively* from body surface measurements anyway.[1] Therefore, it is feasible to define an equivalent generator which produces body surface potentials quantitatively similar to those produced by the actual ventricles. The simplest choice of equivalent generator is a single fixed-location dipole. Several important aspects of the equivalent dipole concept should be emphasized. The heart dipole is a conceptual entity and does not exist in the actual system. While it can be derived, in principle, from the detailed generator, it is extremely difficult to do so practically because of the complexity of the generator and limited knowledge of its detailed operation. (Presently used ideas of simple vector addition for the multitude of dipoles believed to be distributed through the ventricles are unsound.) However, it is relatively easy to determine this hypothetical source from body surface measurements. In principle it is not always possible to obtain a fixed-location dipole which produces precisely the same boundary potentials as any arbitrary set of time varying internal generators.[1]

The degree to which the equivalent representation of the heart as a fixed-location dipole may be applied to ventricular depolarization can be investigated in several ways. The most precise and direct method is mirror pattern cancellations.[2] Experimental existence of nearly exact mirror patterns on the intact human subject, determined by precision cancellation methods, indicates that the fixed-location dipole concept is applicable for the QRS complex to an accuracy of about 5 per cent in most normals.[2, 3] Theoretical estimate is compatible with this experimental result, since a sizable dome-shaped double layer representing a simplified version of ventricular depolarization produces boundary potentials differing by only 5 to 10 per cent from those of an equivalent dipole.[4]

Conducting medium. The assumption of homogeneity is based upon a variety of experimental works. Impedance measurements in living dogs reveal that the resistivity of various body constituents (lung, muscle, liver, kidney, heart muscle) is surprisingly uniform, approximately 1000 $\pm$ 200 ohm-cm. at heart frequencies.[5] Kaufman and Johnston[6] obtained quantitatively different results which were disturbed by electrode polarization. Model studies of the relation between surface potentials and immersed dipoles have shown that the introduction of inhomogeneities exerts a small influence. Gabor and Nelson[1] found that lung resistivity equal to four times that of the rest of the medium produced effects comparable to their small experimental error, and that insulating ribs and spine, remote from the current source, have minor influence. Surface potentials obtained with homogeneous torso models in this laboratory[7] agree quantitatively, within approximately $\pm$10 per cent or less, with those of Burger and van Millaan[8] for an inhomogeneous torso model. Also, in two-dimensional studies[9] similar insensitivity to inhomogeneities is found. Finally, surface potentials produced by inserted current sources[10] and reciprocally energized humans[11] indicate homogeneous behavior of the conducting medium.

The assumption of a resistive medium also has experimental support. Impedance measurements of various body substances reveals only a small reactive component at heart frequencies[5]. More directly, phase-shift measurements in dogs[12] using a precision differential technique show that reactive effects are negligible at heart frequencies. While there is no doubt that capacitance effects exist in biological substances of which the human is composed, they do not become important except at higher frequencies; fortunately, heart signals are confined to the range 0 to 200 cycles per second.[13] The assumption of a medium boundary the same as that of the human figure cannot be incorrect since air is so good an insulator. However, de-

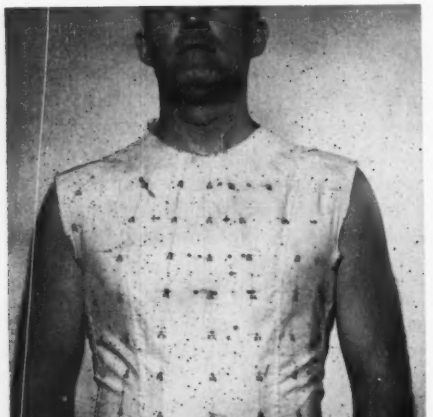

FIG. 1. Front photograph of normal male subject in tailored vest used to locate anatomic points corresponding to points on his torso model. Transverse levels spaced 2 inches apart start with number 3 at the top and continue down to number 11. For each transverse level, 16 points are designated which are equispaced in angle with respect to the vertical anatomic body axis. These angles are designated by letters A through P, with A at the left midaxillary line, E at the front midline, I at the right midaxillary line and M at the back midline. Measurements were confined to levels 3 through 10. Additional marks and holes in the vest were made during the course of the experiments.

tailed shape of the torso is relatively unimportant as has been shown by model studies with male and female torsos,[7, 14] and also by theoretic analysis of a circular chest contour and experimental comparison with a contour in the shape of a typical thorax.[15] The assumption of linearity of the medium is mandatory to develop a sensible theory. While many body substances display electric nonlinear effects when certain thresholds of current density are reached, the current density produced by the heart is comfortably below these levels. Impedance measurements on body substances over a wide range of currents indicate linear behavior.

A Critical Experiment

In order to determine the quantitative accuracy of the foregoing theory, a critical experiment was carried out on a single normal male subject. The critical experiment consisted of a comparison of instantaneous QRS complexes on a normal male subject with results calculated from dipole potentials produced in a homogeneous torso model of the same subject. The experiment was carried out in four phases:

Phase 1: Investigation of the fixed-location dipole representation of ventricular depolarization.

Phase 2: Precision determination of the fixed location of the equivalent dipole in the human subject.

Phase 3: Determination of the instantaneous amplitude of the three dipole components for the QRS complex.

Phase 4: Comparison of measured and calculated instantaneous QRS-complex waveforms over the entire torso.

Throughout all phases great care was exercised in control of posture and respiration of the sitting subject. Anatomic points on the subject corresponding to his torso model points were determined by means of a snugly fitting vest, shown in figure 1, to a precision of about ± 0.5 cm. Electrodes consisted of 27 gage hypodermic needles in all tests.

Phase 1 was undertaken to examine separately errors traceable to the dipole hypothesis itself, as distinguished from other errors such as those traceable to the homogeneity assumption. The method employed was based on a finely detailed study of mirror patterns using a four-electrode precision cancellation technique,[3] a generalization of Schmitt's system.[2] The existence of exact mirror patterns and perfect cancellation is predicted theoretically from the fixed-location dipole hypothesis; in practice, the degree to which QRS complexes lack this exact mirror property is a quantitative measure of the nondipolar content of body surface potentials. A description of the method, technics, experimental errors, basic theory and

results for the male subject investigated has been presented elsewhere.[3]

It was essential to undertake phase 2 because it had been observed in homogeneous torso models that the location of the immersed dipole exerted a pronounced influence on torso surface potentials. It became obvious that calculations from the model could not be expected under any circumstances to agree closely with measured QRS complex waveforms unless the dipole location in the model corresponded very closely with the center of ventricular depolarization in the human subject. A precision method[15] was devised to determine the ventricle center, based on a unique property of dipole potentials produced around the chest at the anatomic level of the ventricles. Potentials at this anatomic level are essentially independent of the head-foot component of the dipole over a wide range of eccentricities characteristic of those expected in humans. The four-electrode cancellation scheme of phase 1 was arranged for obtaining numerous cancellations at the transverse level of the ventricles and cancellation data were matched, independent of waveform, with torso model data in which the dipole location was known, as described in detail elsewhere.[15]

With the dipole location established it was possible at this stage to determine the influence of inhomogeneities by quantitative comparison in three dimensions of human cancellation data in phases 1 and 2 with predictions from the homogeneous model. Because the results were in rather abstract form, phases 3 and 4 were utilized to illustrate in more tangible terms the composite effects of both dipole and inhomogeneity discrepancies between theory and measurement, but additional experimental errors are introduced in the process.

Phase 3 consisted of recording a series of specially selected bipolar leads with equipment of broader band width (400 cycles per second), higher amplification and faster paper speed than ordinarily used. The equipment consisted of a differential preamplifier possessing excellent common-mode rejection characteristics feeding a high-gain amplifier which drove a Hathaway mirror-galvanometer recorder. Since the dipole location in the homogeneous torso model had been established in phase 2 for the subject under test, numerous bipolar leads at a wide variety of sites on the torso model could be specified which would bear a known proportionality to only one component of the dipole. In other words, the torso image surface was known from which "pure" bipolar leads could be selected for measurement of the separate dipole components, in a manner previously described.[16] Six pairs of model points for each dipole component were selected arbitrarily and records of bipolar leads at corresponding anatomic points of the human subject were made. These 18 measurements are included among the total cases given later.

Phase 4 consisted of additional high-gain, high-speed records. Bipolar leads consisted of "pure" dipole component leads, several leads of commonly used systems of vectorcardiography, and random bipolar leads. Unipolar leads were recorded with respect to a two-resistor terminal specially designed for the subject which was within ± 0.2 mv. of the electrical center of ventricular depolarization. Unipolar measurements covered the entire torso, extending from about 2 inches below the neckline to about 2 inches below the belt line (see fig. 1 caption). A total of 190 bipolar and unipolar leads were recorded and analyzed. A typical two-channel record is given in figure 2. In all cases lead II was recorded and the peak of its R wave was taken as zero time for the purpose of synchronizing all records.

Results and Analysis

The results of extensive cancellation experiments in phase 1 in which 38 independent cancellations on the same subject were obtained for anatomic points dispersed widely over the entire torso including in many cases one, and sometimes two, precordial electrodes, have been presented in detail.[3] Directly measured and highly amplified maximum instantaneous potential differences between two QRS complex mirror patterns was typically 0.05 to 0.1 mv. while the complexes themselves ranged from about 1 to 5 mv. The results indicate that the fixed-location dipole hypothesis entailed errors which average 5 per cent for the QRS complex

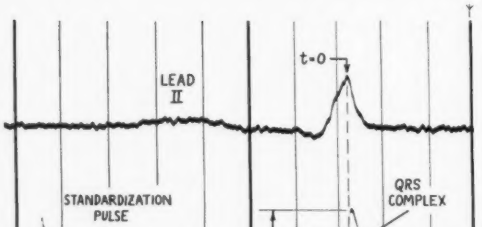

FIG. 2. Typical two-channel record taken during phases 3 and 4. The paper speed is approximately 430 mm per second in this case. Lead II was always recorded on the upper trace and the peak of its R wave was used to establish a time reference, t = 0, common to all records. The 1 mv. standardization pulse was introduced in all records. Construction of the t = 0 reference and subdivision of the 0.04 second timing-line spacing into equal units of 5 milliseconds each are indicated. The baseline is drawn from the start to the end of the QRS complex.

of this normal subject, and no correlation was found with anatomic location of the electrodes.

The results of cancellation experiments around the chest at the transverse level of the ventricles in phase 2 for the purpose of determining the electrical location of the dipole associated with ventricular depolarization have also been presented.[15] The dipole location for "normal" respiration was determined within an estimated error of ±0.5 cm. anatomically. The location for the subject tested was midway between levels 5 and 6 (see fig. 1), 2.1 cm. (6.4 per cent of thorax width) to the left of the sagittal plane containing front and back midlines (angles E and M, respectively), and 4.7 cm. (18.8 per cent of thorax depth) forward of the frontal plane containing right and left midaxillary lines (angles I and A, respectively). This location agreed within 1.5 cm. with the anatomic center of the ventricles estimated by fluoroscopic examination. A byproduct of these studies also permitted construction of a two-resistor terminal[15] whose potential was within ±0.2 mv. of the electrical center of ventricular depolarization. The potential difference between an electrode on the body and this specially devised junction for the particular individual tested is termed the "true" unipolar potential in this paper. While it was not essential to make unipolar measurements in carrying out this critical experiment, it was felt to have certain theoretical niceties such as making a direct record of the Wilson central terminal, which has been published.[15]

The method of analyzing records in phases 3 and 4 may be explained with the help of figure 2. First, the peak of the R wave in lead II was used to establish a common point in time for all records. Next, the 0.04 second intervals between the timing lines were subdivided into 8 equal intervals of 5 milliseconds each. A baseline was drawn through the start and end of the QRS complex, as indicated, and graphical measurement of the amplitude of the QRS complex with respect to this baseline was made at each 5 millisecond interval. The data were converted to millivolts by measuring the ratio of the 1 mv. standardizing pulse amplitude to the peak-to-peak amplitude of the recorded QRS complex.

Final results of the QRS dipole determinations are presented in figure 3 in terms of individual components and heart-vector loops. It may be seen that the duration of the QRS complex is 0.085 second for this individual and that the QRS loop lies essentially in a plane. The dipole components are given in absolute units (ma-cm.) based on the assumption of an average resistivity of 1000 ohm-cm.[5] for the subject. Each component represents the instantaneous average of six independent determinations which were remarkably selfconsistent, and their relative amplitudes are estimated to be accurate to ±10 per cent. The dipole components differ substantially in shape, amplitude and relative timing from deductions made from all systems of vectorcardiography presently in use. The consistency of these results with those predicted from the homogeneous torso model are included in the 190 cases given later.

A total of 190 records were made in phases 3 and 4; 58 bipolar leads and 132 true unipolar leads. The measured peak-to-peak amplitudes

of the QRS complexes in these records ranged from 0.3 mv. to 5.2 mv., distributed as shown in figure 4. The average measured amplitude was 1.57 mv., peak-to-peak.

Calculated instantaneous QRS complexes for each of the 190 cases were obtained using coefficients determined experimentally in a homogeneous torso model of the subject containing a dipole in the location determined in phase 2. Equations were used in the form $V = c_x p_x + c_y p_y + c_z p_z$ in which c_x, c_y and c_z are torso model coefficients[7, 14] which pertain to the particular electrodes in question and p_x, p_y and p_z are given in figure 3 and table 1 which shows a typical calculation. Since the absolute value of the equivalent dipole of the human subject was not known, an overall multiplying factor was determined and applied uniformly to all torso model coefficients such that the average peak-to-peak amplitude of the 190 calculated waveforms was equal to 1.57 mv. volts, the same as that of the measured waveforms. Agreement between individual calculated and measured waveforms was usually quite close and means that the calculated amplitude distribution was very similar to that given in figure 4.

Quantitative comparison of measured and calculated QRS waveforms was made by means of two quantities: per cent amplitude deviation and per cent maximum shape deviation. The per cent amplitude deviation was defined as the difference between calculated and measured peak-to-peak amplitudes expressed as a per cent of the average of the calculated and measured peak-to-peak amplitudes (it can have a maximum possible value of 200 per cent). For example, if the calculated amplitude was 1.1 mv. and the measured amplitude was 1.3 mv. (average equals 1.2 mv.) the per cent amplitude deviation was (1.1–1.3) 100/1.2 = −17 per cent. A positive per cent amplitude deviation indicates that the calculated amplitude exceeded the measured; a negative per cent amplitude deviation indicates that the calculated amplitude was less than measured. The per cent amplitude deviation for 190 cases is given in figure 5 where it may be seen that 92 cases (48 per cent) showed amplitude deviations of ±10 per cent or less, and 142 cases

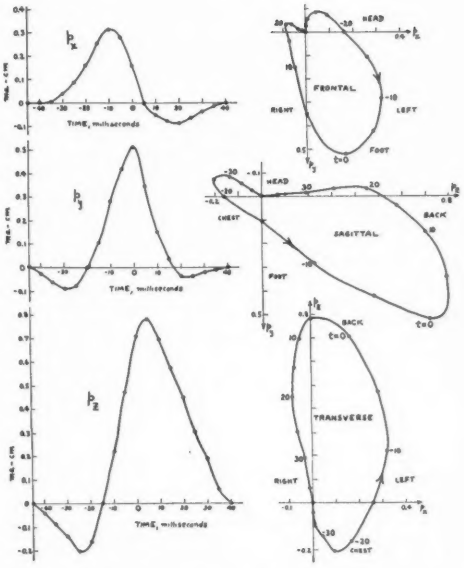

FIG. 3. Final results for the QRS heart dipole component determination are shown for the normal subject tested in terms of rectangular components p_x (right-left), p_y (head-foot) and p_z (chest-back) of the heart dipole and in terms of frontal, sagittal and transverse vector loops. Points on the loops are shown at 5 millisecond time intervals expressed in milliseconds from t = 0, the peak of the R wave in lead II. Dipole components are given in absolute units (ma-cm) based on the assumption of an average resistivity of 1000 ohm-cm[5] for the human torso.

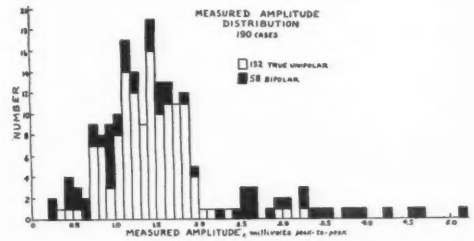

FIG. 4. Measured peak-to-peak amplitude of 190 QRS complexes obtained from a wide variety of electrode sites ranged from 0.3 to 5.2 mv. and were distributed as shown. The average amplitude was 1.57 mv., peak-to-peak. The amplitude distribution of corresponding QRS complexes calculated from dipole potentials in the homogeneous torso model of the subject showed a similar distribution, since their average departure from the measured human complexes was 0.23 mv. The range of unipolar amplitudes was smaller than that of the bipolar.

TABLE 1.—*Sample Calculation of Instantaneous QRS Complex from Homogeneous Torso Model Coefficients*

Time	p_x	p_y	p_z	3.42 p_x	−1.40 p_y	2.56 p_z	V_{QRS}
millisec.	*ma-cm*	*ma-cm*	*ma-cm*	*mv*	*mv*	*mv*	*mv*
−45	0	0	0	0	0	0	0
−40	0	−0.03	−0.04	0	0.04	−0.10	−0.06
−35	0.01	−0.06	−0.09	0.03	0.08	−0.23	−0.12
−30	0.04	−0.09	−0.14	0.14	0.13	−0.36	−0.09
−25	0.09	−0.08	−0.20	0.31	0.11	−0.51	−0.09
−20	0.16	0	−0.16	0.55	0	−0.41	0.14
−15	0.26	0.10	0	0.89	−0.14	0	0.75
−10	0.32	0.28	0.22	1.09	−0.39	0.56	1.26
−5	0.28	0.42	0.47	0.96	−0.59	1.20	1.57
0	0.16	0.52	0.71	0.55	−0.73	1.82	1.64
5	0	0.35	0.78	0	−0.49	2.00	1.51
10	−0.05	0.15	0.70	−0.17	−0.21	1.79	1.41
15	−0.08	0.04	0.58	−0.27	−0.06	1.48	1.15
20	−0.09	−0.04	0.45	−0.31	0.06	1.15	0.90
25	−0.06	−0.04	0.31	−0.21	0.06	0.79	0.64
30	−0.04	−0.02	0.19	−0.14	0.03	0.49	0.38
35	−0.01	−0.01	0.06	−0.03	0.01	0.15	0.13
40	0	0	0	0	0	0	0

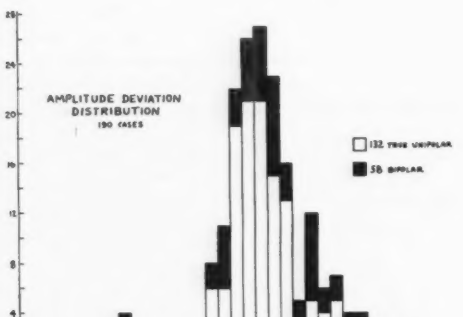

FIG. 5. Amplitude deviation, the difference between measured and calculated QRS complex amplitudes expressed as a per cent of the average of the measured and calculated waveforms, was distributed as shown. Sixty-two per cent of the 190 cases fall within experimental error limits of ±15 per cent.

(75 per cent) showed amplitude deviations of ±20 per cent or less. The average deviation is −1 per cent and the average magnitude of the deviation is 16 per cent. The distribution is not normal and there is no significant difference in distribution for the unipolar and bipolar results. These results may also be expressed in terms of a correlation coefficient $r = 0.94$ for 190 cases.

Shape comparison between measured and calculated QRS waveforms is more difficult to express in quantitative terms. Two independent methods were used; one based on a quantitative definition of per cent maximum shape deviation, the other on subjective evaluation of records such as shown in figure 6. Per cent maximum shape deviation is defined in terms of measured and calculated waveforms which are normalized to have exactly the same peak-to-peak amplitude. It is given by the magnitude of the maximum instantaneous difference between the normalized waveforms expressed as a per cent of the peak-to-peak amplitude (it can have a maximum possible value of 200 per cent). The distribution of maximum shape deviation is given in figure 7. It may be seen that 86 cases (45 per cent) showed maximum shape deviation of 10 per cent or less while 155 cases (82 per cent) showed maximum shape deviations of 20 per cent or less. The average deviation is 14 per cent. Subjective evaluation of the records showed rather consistent agreement with this numerical definition as indicated in figure 7. Of the seven possible ratings, from "very good" to "very poor", based on visual examination of superimposed, normalized measured and calculated waveforms as shown in figure 6, the correlation with maxi

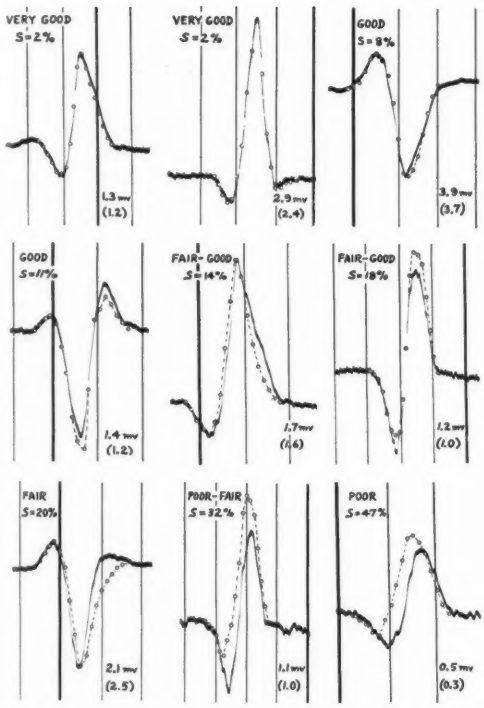

FIG. 6. Measured and calculated QRS complexes are compared for shape agreement by plotting the calculated results on the records with the same peak-to-peak amplitude as the record. Calculated points at 5 millisecond time intervals are shown by small circles, and dashed lines through these points are given when they depart appreciably from the recorded complex. Representative records are shown with both the maximum shape deviation S (in per cent) and the accompanying subjective judgment of the degree of agreement. Measured amplitudes are indicated on each record with corresponding calculated amplitude in parenthesis. All amplitude figures are rounded off to the nearest 0.1 mv. In categories "very good" and "good", 54 per cent of the 190 cases were included, as may be seen in figure 7. A sample of a "very poor" record is omitted since only two cases of the 190 were in this category.

num shape deviation could be made with few exceptions as follows: Very good, 0–5 per cent; Good, 5–11 per cent; Fair to good, 11–18 per cent; Fair, 18–28 per cent; Poor to fair, 28–40 per cent; Poor, 40–60 per cent; Very poor, greater than 60 per cent. The group of representative records in figure 6 gives an idea of the significance of these measures of shape

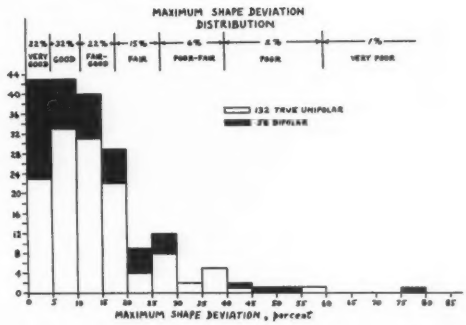

FIG. 7. Maximum shape deviation, defined as the maximum difference between calculated and measured waveforms normalized as in figure 6, expressed as a per cent of the peak-to-peak amplitude of the QRS complex was distributed as shown. Subjective evaluation in the seven categories indicated agreed rather closely with this analytical definition as shown across the top of the diagram. One case (near the left shoulder) showing a maximum shape deviation of 120 per cent is omitted from the diagram. Sixty-six per cent of the 190 cases fall within experimental error limits of ±15 per cent.

agreement. Additional comparisons of measured and calculated waveforms have been presented elsewhere.[15]

Anatomic distribution and correlation between amplitude and shape errors was investigated. The correlation coefficient between per cent amplitude deviation and per cent maximum shape deviation was rather weak, $r = 0.45$. One definite trend was found. Potentials in the vicinity of the left arm were noticeably outside typical deviations, especially in shape. It is not known whether this effect is traceable to inhomogeneities or to a poor representation of the left arm in the torso model, which was capped off rather close to the shoulder. Since there was a steep potential gradient at the root of the left arm of the subject during most of the QRS complex,[17] it is most likely that the average left arm coefficients determined in the model were largely responsible for the disagreement.

DISCUSSION

It has been shown that a theory of electrocardiography based on a fixed-location dipole representation of ventricular depolarization and a homogeneous, resistive linear medium

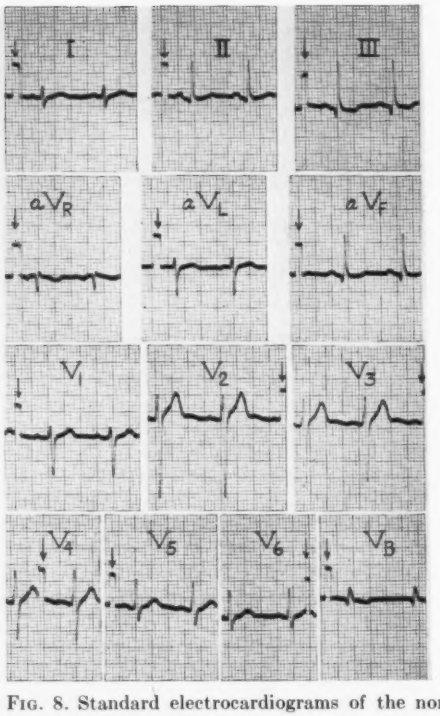

FIG. 8. Standard electrocardiograms of the normal subject tested. Vertical arrows indicate 1 mv. standardization pulse. V_B is the sagittal lead of the Wilson equilateral tetrahedron. Discussion in text is based on high-speed, high-gain synchronous records rather than those given above, in order to obtain more precise quantitative data on amplitude and timing. The potentials given above are included in the 190 cases reported, and were predicted theoretically with satisfactory accuracy.

in the shape of the human torso yields quantitative predictions of instantaneous QRS body surface potentials on one normal subject to an accuracy of approximately ±15 per cent in both shape and amplitude for electrode location dispersed over the entire torso. This accuracy is far better than obtained in present-day electrocardiography which is based on a simpler, qualitative theory. Comparison of the standard electrocardiographic records of the subject tested, shown in figure 8, with the results of this study reveal many significant quantitative differences. Some of these include: (1) The shape of lead I differs markedly from p_x. The ratio of the R to S amplitude is 0.7 for lead I, but 3.6 for p_x. Moreover, lead I crosses the baseline between R and S at a time 15 milliseconds earlier than does p_x. (2) The ratio of R to Q amplitude is 2.2 for V_B, but 3.9 for p_z. Also, V_B crosses the baseline between Q and R at a time 5 milliseconds later than does p_z. (3) While p_y displays a small S wave, this is completely absent in aV_F. (4) Relative peak-to-peak amplitudes of dipole components deduced in this comprehensive study are 1.0:1.5:2.4 for p_x, p_y and p_z, respectively, while those deduced from standard electrocardiograph records are 1.0:2.5:0.8 for corresponding components. (5) Since the Wilson central-terminal potential was 0.8 mv., peak-to-peak, for this subject, amplitude and shape of aV leads differ markedly from true unipolar limb leads. The worse case is V_R which has an amplitude of 0.4 mv. (aV_R divided by 1.5) while the true unipolar right arm potential has an amplitude of 1.0 mv. and an entirely different shape. These examples serve to illustrate substantial deviations between results derived from current practices and those based on an accurate, quantitative theory.

Basic implications of this theory should be clearly recognized. The theoretical system may be described completely by coefficients associated with each boundary electrode[7, 8] and may be interpreted geometrically in terms of an image surface.[8, 16] The coefficients and associated image surface depend upon dipole location and torso shape. They are extremely sensitive to dipole location within the chest.[14, 18] Another basic implication is that there are only three independent data concerning heart generator activity that are obtainable from body surface measurements; the three components of the time-varying dipole. This means that after three independent potential differences are measured, additional leads give only redundant information, in principle. This also implies, as stated previously, that information concerning details of ventricular depolarization is fundamentally inaccessible[1] from body surface measurements in normal subjects and can only be deduced by using additional hypotheses and experimental information not available at the body surface. In addition, this theory implies that "proximity" potentials do not exist at the body

surface in normals; all body surface potentials are derivable from an internal dipole and anatomic proximity to the ventricles is of no fundamental consequence. Finally, use of an indifferent junction which has a potential equal to the dipole midpotential is completely unnecessary; all available information from body surface measurements can be obtained with bipolar leads.

There are many secondary implications of this theory which reveal quantitative errors of current electrocardiographic practices. To illustrate, the Wilson central terminal is seen to depart substantially from the dipole midpotential in this theory.[7, 14, 19] Methods of mean spatial vectorcardiography[20] and vectorcardiography[18, 19] are subject to considerable error in both principle and practice, which interferes with their objective of determining the heart dipole. Recognition of limitations of currently used concepts and practices should spur progress in electrocardiography by giving a meaningful direction to future research which should ultimately lead to more refined clinical methods.

Since dipole potentials produced in homogeneous torso models are closely related to QRS potentials on a normal subject, three dimensional models become a powerful experimental tool for investigating important factors which influence the QRS complex. Extensive studies[7, 14, 16, 17, 18, 19] of such models reveal that the most important single factor in the system is the location of the dipole; so important that if it is not taken into account large errors are inescapable and that if it is taken into account it is probable that other factors such as torso shape and body inhomogeneities would not have to be considered, at least at the outset. It is felt that electrocardiographic practice in which dipole location alone is properly taken into account[18] would represent a major step in improving the accuracy of the determination of the heart dipole from body surface measurements.

Many conflicting (as well as supporting) ideas in connection with the concepts and results presented here may be found in the literature. It is perhaps worthwhile to emphasize that the subject tested was selected by chance and the experiments reported here were conducted with high scientific standards. A careful study of the methods and procedures used reveals many different and unrelated steps at which relatively small errors would have impaired substantially the agreement between theory and measurement. For example, changing the dipole location in the model by only 1 cm. would have approximately doubled the errors in the correlation. Therefore, the correlation obtained cannot be fortuitous, and there is evidence that results on other normal subjects fall within similar quantitative limits of prediction. Moreover, it is known from this study that many factors shown to be of critical importance have been ignored in many other studies, and undoubtedly accounts for some of the conflicting results.

Since flaws in many works may be found in retrospect, it is not unrealistic to expect modern theories to be subject to change in the future. The theory presented here is the simplest which takes all major effects into account in the case of one subject. Because experimental support for the theory presented here is based on only a single normal subject, future modifications may result from investigations of a wide variety of individuals. Moreover, the application of this theory to abnormal subjects has not been investigated comprehensively. Because it has been a general characteristic in science that more refined theories inevitably lead to a sharper focus on the phenomena and a better understanding of the manner in which variables affect the system, it is likely that application of theories of the kind presented will eventually produce this desirable result.

Summary

1. A theory of electrocardiography based on a fixed-location eccentric dipole representation of ventricular depolarization and a homogeneous, resistive linear medium in the shape of the human torso is presented with supporting evidence for the assumptions. Implications of the theory are discussed.

2. A critical experiment is described which tests this theory by quantitative comparison of the instantaneous amplitude and shape of

190 different and independent QRS body surface potentials, over the entire torso of a single normal male subject, with dipole potentials produced in a homogeneous torso model of the same subject. Two-thirds of the results lie within the experimental error of ±15 per cent.

3. It is concluded that dipole potentials in homogeneous three-dimensional torso models are quantitatively related with good accuracy to the QRS complex in normals, and that this represents a theoretical basis for electrocardiography substantially superior to those presently used.

Summario in Interlingua

1. Es presentate un theoria electrocardiographic basate super le assumptiones (a) que le depolarisation ventricular pote esser representate per un dipolo eccentric a location fixe in cata individuo e (b) que le medio intra le qual le currentes cardiac se produce es homogenee, resistive, e linear e que su limites es illos del torso del individuo sub investigation. Datos in supporto del assumptiones facite es presentate. Le implicationes del theoria es discutite.

2. Nos describe un experimento critic que esseva executate con le objectivo de probar le theoria. In le experimento le amplitudes e configurationes de 190 differente e independente potentiales de QRS esseva executate al superficie del integre torso de un sol normal subjecto mascule, e le potentiales assi obtenite esseva comparate quantitativemente con potentiales dipolic producite in un homogenee modello del torso del mesme subjecto. Duo tertios del resultatos se trovava intra le limites de un error experimental de ±15 pro cento.

3. Nos conclude que potentiales dipolic in homogenee modellos tridimensional del torso possede un satis exacte relation quantitative con le complexo QRS in subjectos normal e que iste facto representa un base pro un theoria electrocardiographic notabilemente superior a illos nunc in uso.

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References

[1] Gabor, D. and Nelson, C. V.: Determination of the resultant dipole of the heart from measurements on the body surface. J. Applied Physics **25:** 413, 1954.

[2] Schmitt, O. H., Levine, R. B., Simonson, E. and Dahl, J. Electrocardiographic mirror pattern studies. Parts I, II, III. Am. Heart J. **45:** 416, 500, 655, 1953.

[3] Frank, E.: Measurement and significance of cancellation potentials on the human subject. Circulation **11:** 937, 1955.

[4] —: A comparative analysis of the eccentric double layer representation of the human heart. Am. Heart J. **46:** 364, 1953.

[5] Schwan, H. P., Kay, C. F., Bothwell, P. T. and Foltz, E. L.: Electrical resistivity of living body tissues at low frequencies. Federation Proc. **13:** 131, 1954.

[6] Kaufman, W. and Johnston, F. D.: The electrical conductivity of the tissues near the heart and its bearing on the distribution of the cardiac action currents. Am. Heart J. **26:** 42, 1943.

[7] Frank, E.: General theory of heart-vector projection. Circulation Research **2:** 258, 1954.

[8] Burger, H. C. and van Milaan, J. B.: Heart vector and leads. Parts I, II, III. Brit. Heart J. **8:** 157, 1946; **9:** 154, 1947; **10:** 229, 1948.

[9] Brody, D. A. and Romans, W. E.: A model which demonstrates the quantitative relationship between the electromotive forces of the heart and the extremity leads. Am. Heart J. **45:** 263, 1953.

[10] Powsner, E. R., Nahum, L. H. and Mauro, A.: Body surface potential distribution of an intrathoracic bipole as related to tissue conductivity in electrocardiography. Am. J. Physiol. **177:** 467, 1954.

[11] Schmitt, O. H.: Normalization of vector electrocardiographic axes. Seventh Annual AIEE-IRE-ISA Conference on Electrical Techniques in Medicine and Biology, November 10, 1954, Chicago, Ill.

[12] Goldstein, H. L., Kay, C. F. and Schwan, H. P.: Phase shift in body tissues as it pertains to electrocardiography. Federation. Proc. **12:** 53, 1953.

[13] Gilford, S. R.: High-fidelity electrocardiography. Conference on Electronic Instrumentation in Nucleonics and Medicine, November 1, 1949, New York, N. Y.

[14] Frank, E. and Kay, C. F.: Frontal plane studies of homogeneous torso models. Circulation **9:** 724, 1954.

[15] —: Determination of the electrical center of ventricular depolarization in the human heart. Am. Heart J. **49:** 670, 1955.

[16] —: The image surface of a homogeneous torso. Am. Heart J. **47:** 757, 1954.

[17] —: Absolute quantitative comparison of instantaneous QRS equipotentials on a normal subject with dipole potentials on a homogeneous torso model. Circulation Research **3:** 243, 1955.

[18] —: Analysis of R,L,F,B systems of spatial vectorcardiography. Am. Heart J., in press.

[19] —: A direct experimental study of three systems of spatial vectorcardiography. Circulation **10:** 101, 1954.

[20] — AND KAY, C. F.: The construction of mean spatial vectors from null contours. Circulation **9:** 555, 1954.

[21] — AND —: A reference potential for unipolar electrocardiographic measurements on models. Am. Heart J. **46:** 195, 1953.

APPENDIX I. EXPERIMENTAL ERRORS

Experiments of the kind described are difficult to perform and subject to a wide variety of errors which, altogether, represent a significant portion of the differences between measured and calculated results. Most of these errors are mentioned below and an effort is made to estimate the overall experimental error of this study.

Data obtained on the normal subject was influenced slightly by nonconstancy of posture and state of respiration, despite great care to control these parameters. Throughout the measurements the body was never loaded by resistors smaller than 100,000 ohms but even this sizeable value exerts a slight effect on body surface potentials. The two-resistor terminal used for unipolar measurements had a possible error of ±0.2 mv because of uncertainty of heart dipole location and inhomogeneity effects. The correspondence between factors in the human subject and his model was not perfect: The dipole location error is estimated to be ±0.5 cm, surface electrode locations were not reproducible to better than ±0.5 cm and, in addition, there were larger errors in absolute correlation between model electrode locations and corresponding designations on the vest. The torso shape was obtained by moulding a form to the subject, but this was done about 2 years prior to the experiment and the subject's weight had been reduced by 10 pounds in the interim.

Analysis of the records entailed several errors. Careful examination of figures 2 and 6 shows that the paper speed was not exactly uniform during each QRS complex (slightly different paper speeds are of no consequence) but no attempt was made to correct this; each 0.04 second interval was subdivided into eight equal units. The line width and presence of 60-cycle and muscle-tremor interference led to several errors: (1) Judgment of the exact peak of the R wave in lead II was within an estimated ±2 milliseconds. (2) There was, in some records, a range of different baselines (indicated in fig. 2) that could be drawn for the QRS complex, probably owing to auricular depolarization. An average was usually used. (3) The exact height of the standardization pulse was sometimes difficult to judge to better than ±0.05 mv.

Some of the above errors were estimated in their conglomerate effect by direct measurements. For each record, several complexes were routinely recorded under conditions as constant as practicable. Typical variations from one beat to the next in the same record showed amplitude deviations of ±2 per cent from the mean of several successive complexes and the maximum shape deviation among successive complexes was typically 6 per cent. These results include record analysis errors. Since phases 3 and 4 extended over a period of several weeks, records were made at each session for self-consistency checks with records previously taken. These measurements provide a basis for estimating errors traceable to respiration, physiologic and posture changes and reproducibility of electrode placement. A total of 26 repeat measurements were performed and analyzed; usually about one and one half weeks elapsed between initial and repeated record. Per cent amplitude repeatability was defined as the change in the per cent amplitude deviation from the first record to the repeat record. Per cent shape repeatability was defined as the change in the per cent maximum shape deviation from the first record to the repeat record. These definitions are meaningful measures of amplitude and shape reproducibility since the calculated waveform with which they are compared in each case is the same. Amplitude and shape reproducibility was ±5 per cent or less for 75 per cent of the repeat cases.

In addition to the errors mentioned above, there were also errors inherent in the calculated QRS complex waveforms. The dipole components used in these calculations, as shown in table 1, were average values of a group of independent determinations, and high-frequency detail was smoothed out. The torso model coefficients have an estimated uncertainty of ±5 per cent traceable to many factors such as reference potential drift, distortion caused by the dipole rod support and others which have been discussed previously.[21] In addition the dipole location in the model was probably not exactly in the optimum location for best agreement between calculated and measured results.[17]

An appraisal of all of these factors suggests that an overall experimental error of ±15 per cent is not an unreasonable estimate and in fact represents satisfactory accuracy achievement for this type of investigation. Thus, it may be concluded that approximately two-thirds of the measured and calculated results agreed within the estimated experimental errors.

A Study of the Spatial Vectorcardiogram in Subjects with Posterior Myocardial Infarction

By G. E. Burch, M.D., Leo Horan, M.D., J. A. Abildskov, M.D. and J. A. Cronvich, M.S.

A study of 45 spatial vectorcardiograms of patients with posterior myocardial infarction revealed a characteristic upward displacement of the early portion of the QRS sÊ-loop. Changes in the later portion of the QRS sÊ-loop may occur as a result of infarction. The possible utilization of such findings in the diagnosis of infarction is discussed.

INTEREST has long been focused upon the relationship between the probable manner of spread of the excitation wave in the human ventricle and the graphic registration of the resulting electric potentials on the body surface.[1, 2, 3] The historical development of the concepts of the electrocardiographic changes associated with coronary occlusion and myocardial infarction was reviewed by Wilson and co-workers[4] in 1933, and the association of Q_1 with anterior myocardial infarction and Q_3 with posterior infarction, now commonly accepted, was emphasized at that time. Repeated attempts have been made to link the mean instantaneous electric vectors responsible for the early portion of the QRS complex with specific anatomic sites in records from both normal subjects and patients with posterior myocardial infarction.[1, 5, 6, 7, 8] Attention has been directed to the early portion of the QRS complex, perhaps largely because an empiric clinicoelectrocardiographic correlation is more consistently demonstrated in this portion.[9, 10] The belief that the abnormal Q may result from a delay in conduction which transfers certain electric activity in the depolarization process from its time of normal occurrence in the QRS complex before infarction to a later time in the QRS after infarction[5] may have further directed attention away from later phases of the depolarization process for signs of infarction.

This study was undertaken to describe some aspects of the pattern of the spatial vectorcardiogram in 45 patients with posterior myocardial infarction. Since the spatial vectorcardiogram presents the mean spatial instantaneous electric vectors produced by depolarization and repolarization of the heart muscle, it is possible that the spatial vectorcardiogram can assist in better understanding of modifications of the electrical activities which occur with infarction of the ventricular myocardium.

Because the time course of migration of the process of depolarization is such as to activate certain portions of the ventricular musculature early and other portions later, infarction of those areas that are depolarized late would not be expected to produce alterations in the early portion of the trace, but rather in the late phases. For example, it appears that the region of the conus of the right ventricle and the posterobasal and subepicardial regions of the left ventricle usually are activated last. Therefore, the recorded wave of depolarization in this instance would not be expected to be altered in its early portions but rather in the more terminal portions. The time courses of the magnitude and spatial direction of the mean instantaneous vectors are presented in such detail in the spatial vectorcardiogram that it is possible that this type of recording may

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reveal alterations as a result of infarction involving regions activated late or intermediate in time. These aspects of the data were particularly studied. In addition, other aspects of configuration of the spatial vectorcardiogram were observed, in an attempt to describe certain of its characteristics in posterior myocardial infarction.

Materials and Methods

Forty-five patients in whom the diagnosis of myocardial infarction of the posterior or diaphragmatic surface was considered likely have been studied. These included 37 men and 8 women, ranging in age from 44 to 85 years. Thirty-seven included in this study had clinical histories suggestive of myocardial infarction, and 33 patients had electrocardiograms showing evidence of acute infarction a few weeks to several years prior to this study. The remaining 11 patients had electrocardiograms showing Q waves and abnormal T waves in leads II and III at the time of this study which, in association with suggestive clinical data, were considered to have sufficient evidence of posterior infarction to be included in this series. Three patients died, and the presence of posterior infarction was confirmed at autopsy.

The spatial vectorcardiograms were recorded with the equilateral tetrahedral system of electrode placement by means of methods previously reported.[11] Projections of the spatial vectorcardiogram on the frontal, right, left, and superior planes of the reference frame as well as projections on the left surface midplanes perpendicular to these were recorded. The respective perpendicular plane projections were recorded in simultaneous pairs. Stereoscopic views of the projections on each of the plane surfaces of the tetrahedron were also obtained.

Electrocardiograms were obtained immediately after the vectorcardiograms were recorded. These included standard leads, bipolar leads formed by the electrode on the back with those on the limbs, unipolar leads from the points defining the apices of the tetrahedron, and precordial leads V_1 through V_6. Proper pairs of standard and unipolar limb and back leads were recorded simultaneously so that any portion of any lead could be oriented temporally with respect to selected portions of the other leads. Recordings of both electrocardiograms and vectorcardiograms were obtained with the patients in the supine position, with the head elevated approximately 20 degrees from the horizontal plane.

Three-dimensional wire models of the spatial vectorcardiograms were constructed to conform to the contour of the plane projections of the vectorcardiograms. These models and the recorded plane projections and stereoscopic views were studied with respect to the general and detailed configurations and to the spatial orientation of the QRS sÊ and sÊ-loops. Special attention was given to differences in orientation and configuration between the QRS sÊ-loop of normal subjects and the QRS sÊ-loop of patients with left ventricular enlargement or other cardiac states. Measurements of the length and direction of the maximal instantaneous QRS and T vectors in the frontal and left sagittal plane projections are presented to assist in defining the general range of spatial orientation and size of the loops.

Results

QRS sÊ-loops

Forty-one of the records were divided into two groups, A and B, on the basis of similarity in form of the QRS sÊ-loops. Four records constituted a miscellaneous group in which there was no consistent configuration of the QRS sÊ-loops.

Group A: Twenty-six records were characterized by upward displacement of the early part or all of the efferent limb and by an afferent limb which tended to resemble that of normal records in general contour and spatial orientation. A record that is representative of this group is shown in figure 1.

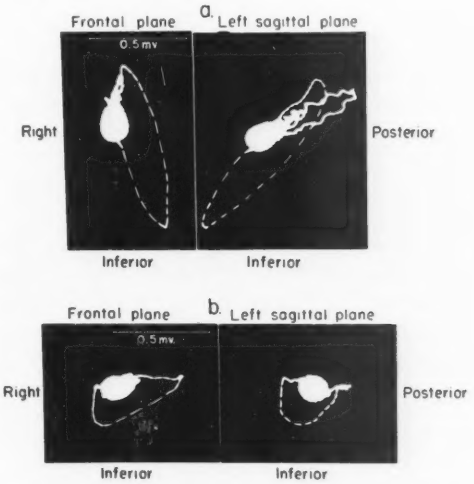

Fig. 1. Frontal- and left sagittal-plane projections of examples of QRS sÊ-loops resembling the two normal types[11] of two patients with posterior myocardial infarction, showing displacement of the early portion of the efferent limb. The QRS sÊ-loop shown in *a* resembles the QRS sÊ-loop of normal type 1 and that in *b* resembles the normal type 2.

In the illustrations to follow, *Right*, *Inferior* and *Posterior* refer to the subject.

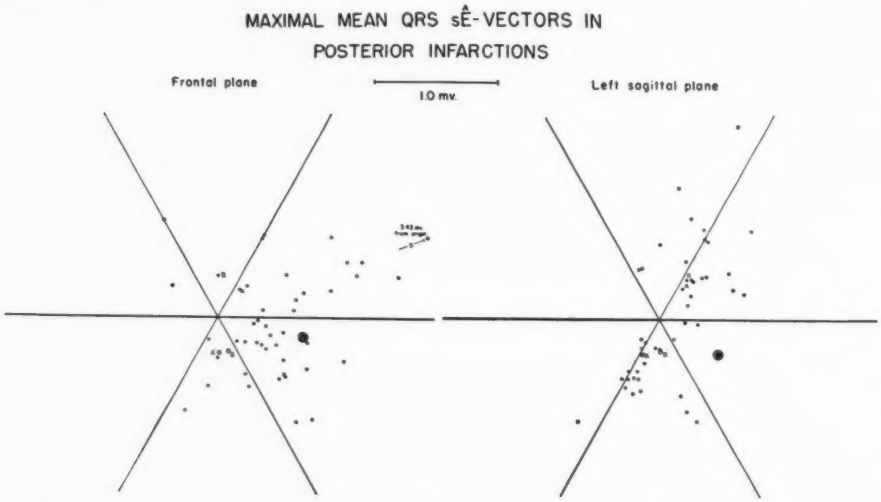

FIG. 2. The location in the frontal and left sagittal planes of the projections of the maximal mean instantaneous QRS sÊ-vectors for all 45 patients with posterior myocardial infarction. The average is represented by the circled dot in each plane. A and B represent the maximal vectors that occurred in the early portion of two loops of group A; A′ and B′ represent the lesser vectors that corresponded more closely temporally with the other maximal vectors of that group. (These two sets of vectors from the respective QRS sÊ-loops were of almost equal magnitude). The scale indicates magnitude in millivolts.

In the frontal-plane projection, 21 of these loops were inscribed in a clockwise direction, whereas five formed figures-of-eight in which the proximal portions were also inscribed clockwise. In the left sagittal-plane projection, six were inscribed in a clockwise and 12 in a counterclockwise direction, whereas eight formed figures-of-eight.

The magnitude and direction of the maximal QRS vectors in the frontal and the left sagittal planes are shown in figure 2. In two of the records the upward displacement of the early portions of the loop was so pronounced that the maximal vectors were located in the first and second sextants of the triaxial reference system in the frontal plane, even though later portions of these loops resembled those of normal subjects. Thus, in figure 2, two vectors are presented to represent each of these records: the maximal vector, in the early portion of the loop, and the smaller, which corresponded more closely temporally with the other maximal vectors.

In table 1 the maximal, minimal and average values of the maximal mean instantaneous vector in this group of records are compared with the values obtained from 75 normal records. It may be seen that the maximal mean instantaneous vectors of the two groups were similarly oriented. In general, the magnitude of the mean instantaneous vectors of the QRS sÊ-loops in this group was less than that of the normal records. With the exception of the upward displacement of the early portion of the efferent limb, the QRS sÊ-loops of this group tended to resemble the normal loops.

Those records that were similar to the type 1 normal records had elliptoid configurations with varying spatial orientations. In seven records the trace in the midportion of the loop moved rapidly from left to right to give a slightly truncated appearance to the QRS sÊ-loops (fig. 3). Those records that appeared more like the normal QRS sÊ-loop previously described as type 2 had more nearly circular spatial contours with a larger enclosed area lying behind the isoelectric point (fig. 1b). The many variations in configuration of the

TABLE 1.—*Maximal QRS sÊ-vectors of 45 Patients with Posterior Myocardial Infarction*

	Projection in Frontal Plane		Projection in Left Sagittal Plane	
	Magnitude (mv)	Angle (degrees)	Magnitude (mv)	Angle (degrees)
*Normal (75)**				
Maximal	1.73	+116	1.47	+129
Minimal	0.31	+20	0.21	−80
Average	0.95	+64	0.83	+99
*Group A: Posterior Infarct (26)**				
Maximal	1.11	+113	1.04	+132
Minimal	0.28	−16	0.19	−167
Average	0.54	+42	0.44	+76
*Group B: Posterior Infarct (15)**				
Maximal	3.42	+32	1.66	+113
Minimal	0.34	−60	0.40	−90
Average	0.99	−17	0.66	−73
All Posterior Infarcts†				
Average (45)*	0.71	+14	0.54	+31

* Numbers in parenthesis indicate number of subjects.

† Includes 4 miscellaneous tracings not grouped under A or B.

plane projections represented variations in spatial orientation of basically similar QRS sÊ-loops.

Group B: Fifteen records were grouped together because of the common characteristics of upward displacement of the portions adjacent to the isopotential point in both the afferent and efferent limbs of the QRS sÊ-loop. By upward displacement is meant displacement largely into the second sextant of the triaxial reference system of the frontal plane.

The degree of upward displacement was more pronounced in the afferent limb in all 11 of these loops, and, thus, the direction of inscription in the frontal plane projection was counterclockwise in all except the four in which figure-of-eight configurations were found. In the left sagittal plane projection, five QRS sÊ-loops were inscribed in a counterclockwise and six in a clockwise direction.

The magnitude and direction of the maximal mean instantaneous QRS vectors in the frontal and left sagittal plane projections are shown in figure 2 and table 1. The major areas conformed roughly in location with the maximal vectors, and, thus, these QRS sÊ-loops were located largely in the first and second sextants of the triaxial reference system of the frontal plane and in the second and third sextants in the left sagittal plane projections. All except one were located almost completely posterior to the isoelectric point. The QRS sÊ-loop in this one record was located in the second sextant in the left sagittal plane but entirely anterior to the isoelectric point.

In addition to the displacement of the initial and terminal limbs, all QRS sÊ-loops in this group were distinguished by an arc-like deformity in the efferent limb with the concavity downward. This deformity produced the overall effect of a sagging, oblong configuration in

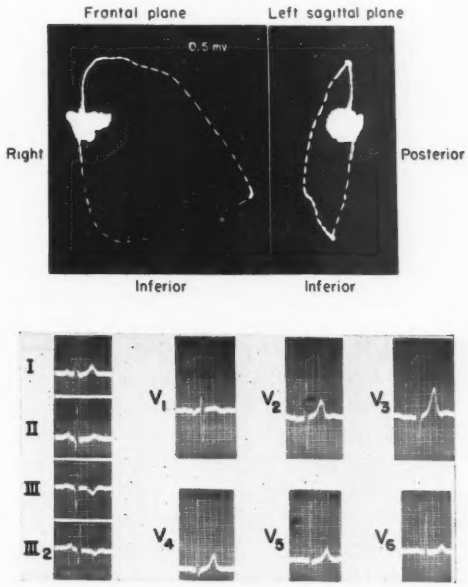

FIG. 3. An example of the QRS sÊ-loop of a patient with posterior myocardial infarction, in which the trace moved rapidly from left to right and also produced a slightly truncated appearance of the QRS sÊ-loop. Note that the accompanying routine electrocardiogram does not suggest an abnormality in the midportion of the QRS complex.

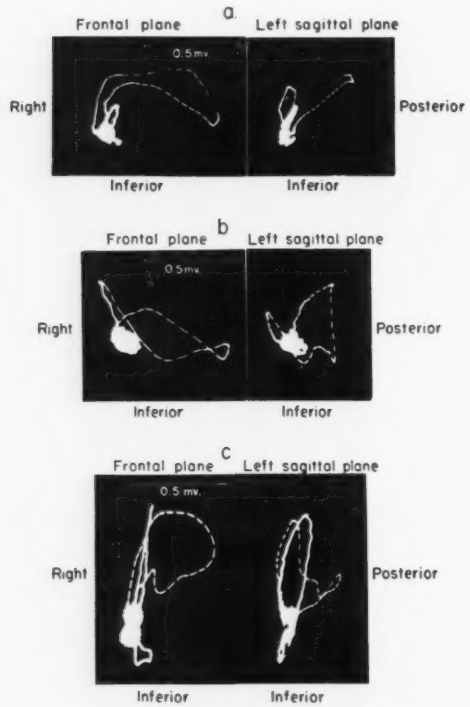

FIG. 4. Examples of the QRS sÊ-loops of three patients with myocardial infarction, in which both the late portion of the afferent limb and the early portion of the efferent limb are displaced upward. Note the upward orientation of the T sÊ-loops in *a* and *c*.

the frontal plane projection except in those examples with a figure-of-eight pattern (fig. 4, *a* and *b*). Four of the 15 QRS sÊ-loops in group B had a greater upward displacement of the early portion of the efferent than that of the late portion of the afferent limb. This resulted in clockwise inscription of the loop in the frontal plane (fig. 4*c*).

Miscellaneous Group: There remained four records with QRS sÊ-loops whose contours could not be classified in groups A or B. These could be removed from immediate consideration because of the presence of a complicating lateral infarction or extension in one and a complicating anterior infarct in the other three. One of the latter three also demonstrated right bundle branch block.

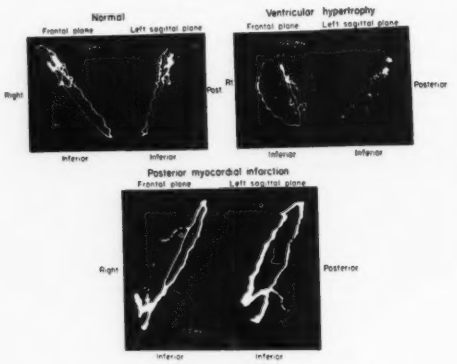

FIG. 5. Examples of typical T sÊ-loops in a young normal adult, a patient with left ventricular hypertrophy, and a patient with posterior myocardial infarction. Consult the text for details.

T sÊ-loops

A distinctive long, narrow, line-like, upwardly directed T sÊ-loop was noted in 19 of the 37 records in which the T sÊ-loops were suitable for study (fig. 5). It was usually directed along the −60 degree axis of the triaxial reference system of the frontal plane projection. In 15 of these the T sÊ-loop in the left sagittal plane projection was directed slightly posteriorly as well as upward and in four, slightly anteriorly. Of the remainder, seven T sÊ-loops appeared similar to the loops in normal subjects whereas 10 were similar neither to normal nor to the typical upwardly directed loops. Eight of these 10 abnormal T sÊ-loops appeared similar to the small, round, open T sÊ-loop described for left ventricular hypertrophy (12). The magnitude and direction of the maximal mean instantaneous spatial vectors of the T sÊ-loops are shown in figure 6.

DISCUSSION

During the course of analysis of the spatial vectorcardiograms, it became evident that the term "initial" mean instantaneous spatial vector of the QRS sÊ-loop was difficult to define and often even more difficult to locate. Because of muscular tremor, interfering currents, and other artifacts, it was not possible to determine with certainty in most, if not all,

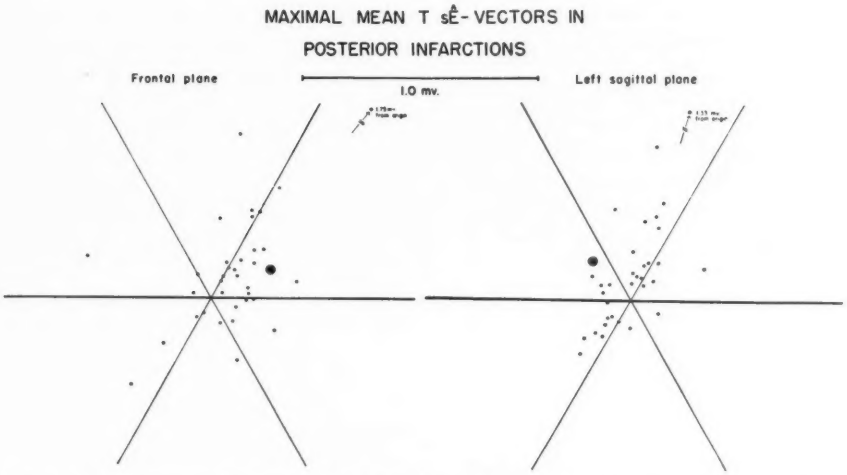

FIG. 6. The location in the frontal and left sagittal plane of the projections of the maximal mean instantaneous T sÊ-vectors for 34 patients with posterior myocardial infarction. The mean is indicated by the circled dot in each plane. The magnitude in millivolts is indicated by the scale.

records the "first" vector of the QRS sÊ-loop. By connotation, the initial mean instantaneous vector is the first one. Since it was not possible to identify with certainty the first one, the "early," definitely identifiable vectors were studied. Although no specific time in the cycle of the QRS sÊ-loop was considered in these studies, the early vectors most probably occurred during the first 0.04 second of ventricular depolarization. It is also well to note that the truly initial vectors may not be concerned with or influenced by the infarcted areas, a problem yet unsolved.

Characteristic changes in the early portions of the QRS complex and QRS sÊ-loop as a result of myocardial infarction are well known from studies in electrocardiography.[4, 8, 9, 10] It is likely that changes in later portions of these complexes also occur, but these have been neglected. This has been attributed, at least partially, to the rather wide variability of the later portions of the QRS complexes. A similar wide variability in orientation but not in configuration of QRS sÊ-loops in the normal and in certain abnormal states has been noted. For example, it was found that all of a series of QRS sÊ-loops in young normal adults could be classified into two groups on the basis of contour.[11] It has also been found that QRS sÊ-loops typical of left ventricular hypertrophy have a relatively constant and characteristic contour.[12] The relatively few variations in the configuration of normal and some abnormal QRS sÊ-loops may facilitate detection of the effects of infarction in later portions of the depolarization process.

In this series, the early portion of the QRS complex and the QRS sÊ-loop were altered as compared with the normal in all instances, since this was one of the criteria for selection of cases. In some QRS sÊ-loops, as far as could be determined, only the early portion had been altered by infarction, whereas other traces presented alterations of later portions of the loop as well, which could be assumed to have been the result of infarction. The frontal plane vectorcardiogram in a patient with posterior myocardial infarction described by Wilson and Johnston probably belonged to this group.[13] For example, in the instance of the QRS sÊ-loop of figure 3, infarction or death of an area of myocardium which normally would have been activated midway in time during ventricular depolarization most probably resulted in loss of the manifested electric vectors of depolarization and, thereby, in distortion of

the QRS sÊ-loop at that moment. Although this theoretic concept supported by indirect evidence seems obvious, correlations with carefully studied postmortem data are necessary to establish the validity of the concept. It is well to note that the electrocardiogram (fig. 3), at least, recorded at standard paper speed 25 mm. per second failed to disclose evidence of distortion of the later phases of the depolarization process. Such changes in the later portions of the QRS sÊ-loop, most probably due to the location of infarcts, were noted for eight subjects, whereas the conventionally recorded electrocardiogram failed to reveal the distortions.

In general the change in the QRS sÊ-loop which is to be expected in diaphragmatic surface infarction is the appearance of more and larger vectors directed upward.[4, 7, 14, 15, 16, 17, 18] This change is seen in its simplest form in the records described as group A. Here the major alteration appears to be in the initial portion of the QRS sÊ-loop. Except for that portion directed upward to the frontal projection, these QRS sÊ-loops might be considered to resemble those of the normal in orientation and general contour. Theoretically, these vectors might also be directed anteriorly or posteriorly, depending on the location of the infarct on the diaphragmatic surface of the heart, and, in contrast to other studies,[19] considerable variation in the upward direction of these vectors was observed.

The form and orientation of the QRS sÊ-loops of group B can be explained mainly on the basis that infarction of the diaphragmatic surface of the heart produced varying degrees of upward displacement of both afferent and efferent limbs. Upward displacement of the afferent limb, however, may be due to infarction of the posterior and basal regions of the left ventricle which are depolarized late in the electrical systolic cycle (fig. 4). Left ventricular hypertrophy alone or in association with a posterior basal infarct may have also deviated the terminal portion of the afferent limb superiorly or upward.

It is interesting to note that infarction did not necessarily obscure the vectorcardiographic features of left ventricular hypertrophy. Conversely, the arc-like appearance of the efferent limb of these QRS sÊ-loops was not encountered in a series of records from patients with typical vectorcardiographic characteristics of left ventricular hypertrophy without clinical and electrocardiographic evidence in infarction.

Well known theoretic considerations in electrocardiography account for the deviation of the mean instantaneous spatial vectors away from the infarcted area (fig. 1). This appeared to be true not only for the early phases of depolarization but for the late ones as well. Apparently, losses of the electric activity of depolarization of a segment of myocardium tended to produce concave distortion in the QRS sÊ-loop (fig. 4).

The T sÊ-loop was spatially oriented essentially parallel to and in the same direction as the early mean instantaneous vectors of the QRS sÊ-loop (figs. 4 and 6). This would be expected from existing electrocardiographic knowledge of the changes and the mechanism for their formation in infarction. Because these records were obtained at widely varying intervals following development of the infarct, this relationship between the T sÊ-loop and the QRS sÊ-loop varied from the typical in many instances.

Summary

(1) The spatial vectorcardiograms of 45 patients with posterior myocardial infarction have been studied and described.

(2) The spatial vectorcardiogram in posterior myocardial infarction differed from the normal. The initial portion of the efferent limb of the QRS sÊ-loop in all instances, except one, showed a characteristic upward displacement; there was an additional upward displacement of the afferent limb in many instances. Many records displayed a long, line-like T sÊ-loop directed upward and to the left, corresponding to the negative T_3 pattern observed in the conventional electrocardiogram.

(3) The possibility of utilizing data obtained from the later vectors of depolarization has been discussed.

(4) Further study, especially with postmortem correlation, is required to ascertain

the clinical and diagnostic value in posterior myocardial infarction of the additional data available in the spatial vectorcardiogram not detectable in the electrocardiogram with the use of the conventional standard and chest leads.

SUMMARIO IN INTERLINGUA

1. Esseva studiate e describite le vectocardiogrammas spatial de 45 patientes con infarcimento myocardial posterior.

2. Le vectocardiogramma spatial in infarcimento myocardial posterior differeva ab le norma. Le portion initial del membro efferente del spira QRS sÊ monstrava in omne casos, con un exception, un characteristic displaciamento in alto. In multe casos il habeva additionalmente un displaciamento in alto in le membro afferente. Multe registrationes exhibiva un longe spira T sÊ, orientate in alto e verso le sinistra, correspondente al negative configuration T_3 que se observa in le electrocardiogramma conventional.

3. Es discutite le possibilitate de utilisar datos obtenite ab le vectores ulterior de dispolarisation.

4. Studios additional—specialmente in re correlationes post morte—es requirite pro determinar le valor clinic e diagnostic representate in casos de infarcimento myocardial posterior per le datos additional que es detegibile in le vectocardiogramma spatial sed que non es detegibile in le electrocardiogramma per medio del derivationes standard e thoracic in uso conventional.

REFERENCES

[1] LEWIS, T.: The Mechanism and Graphic Registration of the Heart Beat. Ed. 3, London, Shaw and Sons, Ltd., 1925.

[2] FAHR, G.: An analysis of the spread of the excitation wave in the human ventricle. Arch. Int. Med. **25:** 146, 1920.

[3] MANN, H.: A method of analyzing the electrocardiogram. Arch. Int. Med. **25:** 283, 1920.

[4] WILSON, F. N., MACLEOD, A. G., BARKER, P. S., JOHNSTON, F. D. AND KLOSTERMEYER, L. L.: The electrocardiogram in myocardial infarction with particular reference to the initial deflections of the ventricular complex. Heart **16:** 155, 1933.

[5] FENICHEL, N. M. AND KUGELL, V. H.: The large Q-wave of the electrocardiogram. A correlation with pathological observations. Am. Heart J. **7:** 235, 1931.

[6] EDEIKEN, J. AND WOLFERTH, C. C.: The incidence and significance of the deep Q-wave in lead III of the electrocardiogram. Am. Heart J. **7:** 695, 1932.

[7] BAYLEY, R. H.: A theoretical genesis of Q as observed in the first three standard leads of the electrocardiogram. A preliminary report. J. Trop. Med. **41:** 144, 1938.

[8] GARDBERG, M. AND ASHMAN, R.: The QRS complex of the electrocardiogram. Arch. Int. Med. **22:** 210, 1943.

[9] BAYLEY, R. H.: The significance of the duration of Q_3 with respect to coronary disease. Am. Heart J. **18:** 309, 1939.

[10] DEN BOER, W.: The clinical value of vectorcardiography. Acta med. scandinav. **154:** 217, 1952.

[11] BURCH, G. E., ABILDSKOV, J. A. AND CRONVICH, J. A.: Studies of the spatial vectorcardiogram in normal man. Circulation **7:** 558, 1953.

[12] HORAN, L. G., BURCH, G. E., ABILDSKOV, J. A. AND CRONVICH, J. A.: The spatial vectorcardiogram in left ventricular hypertrophy. Circulation **10:** 728, 1954.

[13] WILSON, F. N. AND JOHNSTON, F. D.: The vectorcardiogram. Am. Heart J. **16:** 14, 1938.

[14] FERRERO, C., DORET, J. P. AND GAY, E.: Contribution au diagnostic de l'onde Q_3, étude vectorgraphique. Cardiologia **20:** 47, 1952.

[15] WENGER, JON R. AND DONEFF, D.: Vektorkardiographische Untersuchungen bei Herzmuskelinfarkt. Cardiologia **22:** 303, 1953.

[16] SCHERLIS, L. AND GRISHMAN, A.: Spatial vectorcardiography: myocardial infarction. V. Am. Heart J. **42:** 24, 1951.

[17] DUCHOSAL, P. W. AND SULZER, R.: La Vectorcardiographie. Basel, S. Karger, 1949.

[18] BURCH, G. E., ABILDSKOV, J. A. AND CRONVICH, J. A.: Spatial vectorcardiography. Philadelphia, Lea and Febiger, 1953.

[19] MILNOR, W. R., GENECIN, A., TALBOT, S. A. AND NEWMAN, E. V.: A vectorcardiographic study of the Q_3 deflection in cases of myocardial infarction and in normal subjects. Bull. Johns Hopkins Hosp. **81:** 281, 1951.

Vectorcardiographic Investigations on the Auricles

By Rudolf Wenger, M.D., Klemens Hupka, M.D. and Erwin Wick, M.D.

Vectorcardiography demonstrates very clearly the method of auricular activation and shows its spatial development. This is illustrated and discussed in this paper as it occurs in normal subjects, in a patient with an ectopic auricular pacemaker, and in patients with pulmonary heart disease. Changes similar to those seen in patients with cor pulmonale have been observed in dogs after partial occlusion of the pulmonary artery. Remarkable alterations of the auricular vectorcardiogram have been seen in patients with mitral heart disease after commissurotomy.

SINCE THERE IS NO FINAL AGREEMENT concerning the methods which should be used in vectorcardiography, the vectorcardiograms, registered by various investigators, are, therefore not absolutely comparable. In Vienna we use the method of Polzer and Schuhfried.[1] By this method the normal auricular vector loops are directed anteriorly and inferiorly. The sense of rotation is counterclockwise in the frontal and horizontal, and clockwise in the sagittal plane. Theoretically, the auricular vectorcardiogram may be subdivided into a partial vectorcardiogram of the right and a partial vectorcardiogram of the left auricle. The isolated vectorcardiogram of the right auricle would mainly be directed inferiorly, whereas the isolated left auricular vectorcardiogram would be directed mainly to the left, which corresponds to the main direction of activation of the left auricle.

Figure 1 shows the vectorcardiogram of a normal subject. On all illustrations a potential of 1 mv. corresponds to a deflection of the vectorcardiographic loop of 2 cm.

Vectorcardiograms in Conditions Associated with Auricular Abnormalities

Mitral Stenosis. In mitral stenosis the time of activation of the left auricle is prolonged if the auricle is dilated. Therefore the P waves are notched and broader than normal in leads II and III. The ratio P-Q/i-Q, obtained by the use of standard and esophageal leads, is increased. The atriodiagram for the left auricle shows a bulge. Both these methods have been described elsewhere in detail.[3-5]

The frontal auricular vectorcardiogram often shows a distortion of the loop, corresponding to the deformity of the P waves in standard leads II and III. The horizontal loop likewise shows typical changes. In most cases the vector loop is diphasic. The first part of the vector loop, which is partly produced by the normal right auricle activated alone before the left auricle is activated, is directed anteriorly. The second part, which is related to the dilated left auricle with prolonged activation, is directed posteriorly and shows a clockwise rotation (fig. 2*A*). In connection with this deviation of the second part of the horizontal vector loop, it is to be noted that the direction of the dilatation of the left auricle is mainly toward the left and posteriorly.

In severe cases of mitral stenosis, the horizontal vector loop is directed entirely posteriorly. It shows a clockwise rotation (fig. 2*B*). This vectorcardiogram was taken from a 52 year-old patient with mitral heart disease of long duration. In this case, the sagittal vectorcardiogram also shows very clearly the deviation of the second part of the auricular vector loop in the posterior direction.

We investigated 23 patients with mitral stenosis who underwent commissurotomy. In six cases studied after operation, the auricular vectorcardiogram was not altered essentially. In the remaining cases, a distinctive change of the horizontal auricular vectorcardiogram occurred: the vector loop, which had been

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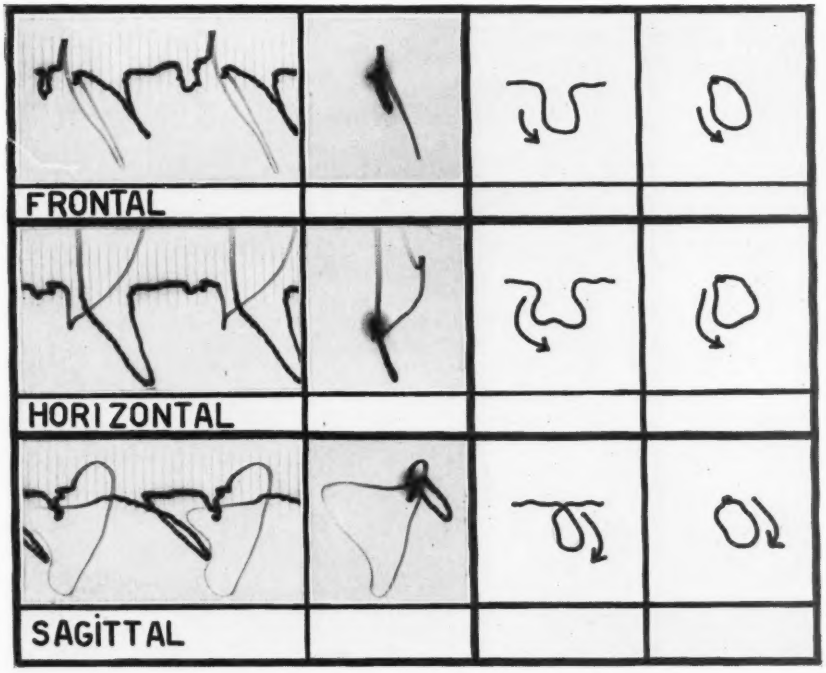

FIG. 1. M. A., a 25 year-old man. Normal subject.

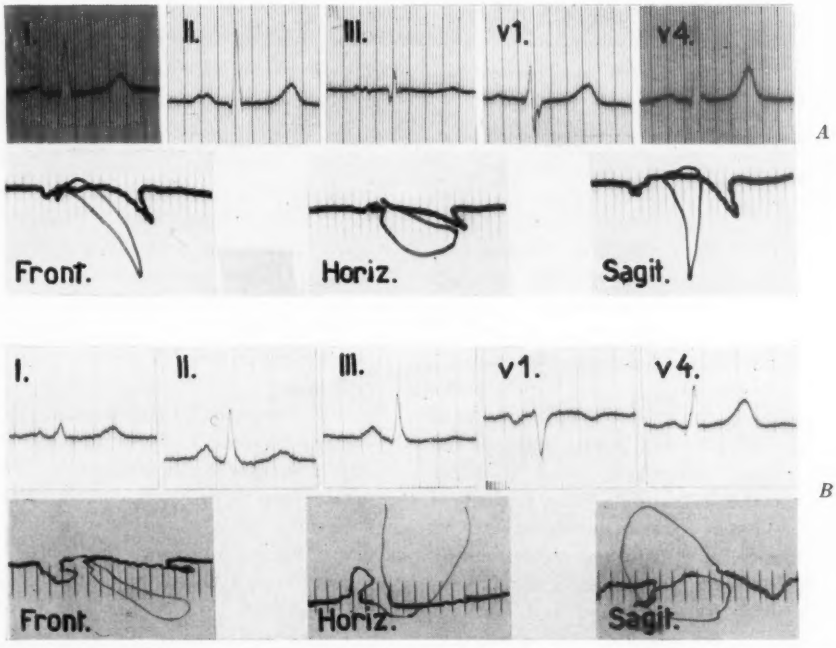

FIG. 2*A*, E. G., a 23 year-old man with mitral stenosis of a moderate degree. *B*, K. L., a 52 year-old man with mitral stenosis of a severe degree.

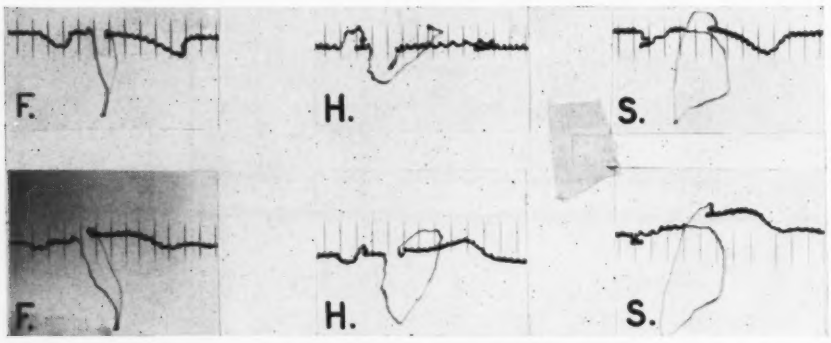

FIG. 3. P. A., a 25 year-old man with mitral stenosis. *A*, shows preoperative and *B*, postoperative loops.

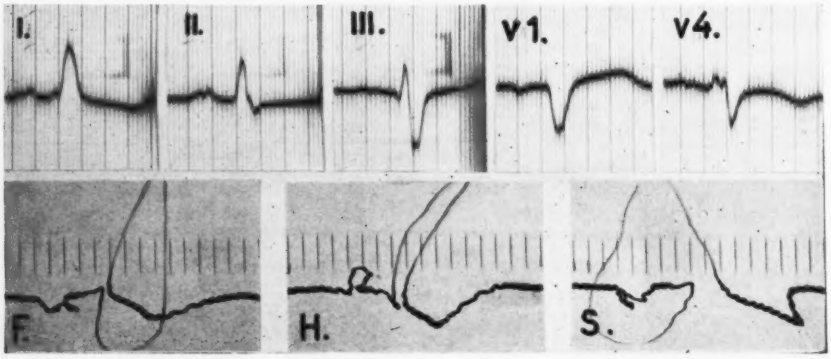

FIG. 4. M. K., a 49 year-old man with hypertrophy of the left ventricle

directed partly or totally posteriorly before operation, was directed more anteriorly or completely anteriorly after operation. Also, the direction of rotation, which before operation was clockwise in the posteriorly directed part of the vector loop, was changed after operation and showed a counterclockwise rotation. Figure 3*A* shows such changes in the auricular vectorcardiogram after commissurotomy.

Left Ventricular Hypertrophy. Corresponding changes of the auricular vector loop may also be seen but rarely in patients with marked left ventricular hypertrophy and resulting dilatation of the left auricle. The patient of figure 4 is a 49 year-old man, suffering from an obliterative arterial disease and corresponding changes of the coronary vessels. The left ventricle is grossly hypertrophied and the left auricle dilated. The ventricular electrocardiogram and vectorcardiograms show widening of QRS and changes due to enormous left ventricular hypertrophy. The auricular vectorcardiogram in the horizontal plane shows clockwise rotation and marked posterior deviation, similar to the changes observed in cases of severe mitral stenosis.

Cor Pulmonale. In patients with pulmonary heart disease, the P waves are prominent and peaked in leads II and III. The right auricle is hypertrophied. Corresponding to the increased bioelectric forces causing the partial right auricular vectorcardiogram, the auricular vector loop is directed mainly inferiorly and anteriorly. This is best shown in the frontal plane. Figure 5*A* shows the vectorcardiogram registered on a 27 year-old woman who has been suffering from bronchial asthma for five years.

Pulmonary Stenosis. We were able to observe

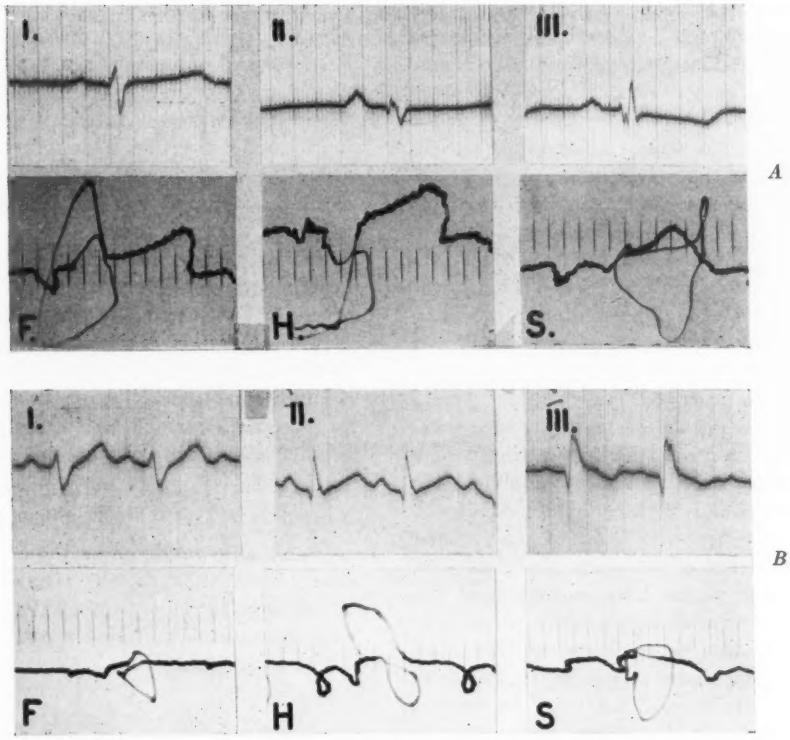

FIG. 5. *A*, K. H., a 27 year-old woman with bronchial asthma. *B*, H. H., a four year-old boy with pulmonary stenosis.

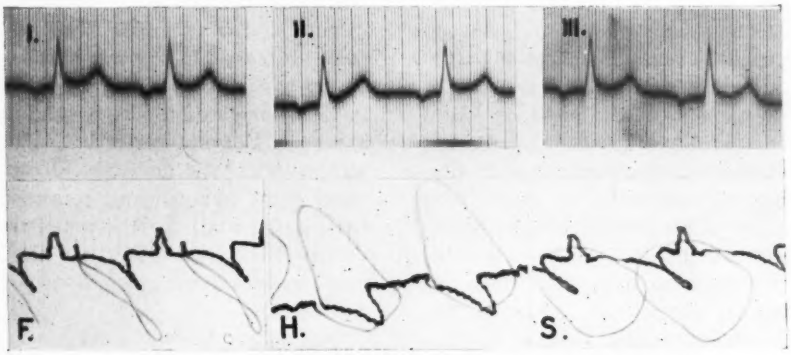

FIG. 6. Sch. M., a 21 year-old man with an ectopic auricular rhythm

similar changes in patients with pulmonary stenosis, in which obstruction in the outflow tract of the right ventricle causes a dilatation and hypertrophy of the right auricle. This is responsible for the higher bioelectric potentials in this part of the heart. The auricular vectorcardiogram shows relatively large, peaked loops, which are best shown in the sagittal plane. The vectorcardiogram shown in figure 5*B* was obtained in a boy 4 years of age.

Animal Experiments. Similar changes of the auricular vector loops were found in animal

experiments. We clamped a portion of the pulmonary artery of the exposed dog hearts and observed a gradual prolongation of the frontal and sagittal vector loops. This development was the result of the higher electric potential which arose in the acutely dilated right auricle.

Ectopic Auricular Pacemaker. Also, in patients with ectopic auricular pacemakers, the direction of the auricular vectorcardiogram is altered characteristically. Figure 6 shows the curves obtained from a 21 year-old man, who showed no evidence of heart disease. The electrocardiogram showed P waves which are directed downwards in leads II, III and aV_F. This case is described elsewhere in detail.[6] The assumption of the existence of a pacemaker situated in the caudal portion of the auricles seemed to be justified. The electrocardiographic pattern is similar to that produced experimentally by Prinzmetal and his co-workers[5] on stimulation of caudal parts of the auricles. The auricular vector loops are deviated upward in the frontal and sagittal plane. The sense of rotation is clockwise in these two planes. The horizontal vectorcardiogram shows a more or less normal pattern. The vectorcardiogram clearly shows that the auricles in this case are activated in a reverse sense.

Comments and Summary

The auricular vectorcardiogram is changed characteristically in many instances of pathological disorders of the auricles. A few examples are given in this paper. In cases of mitral stenosis, the altered partial vector of the left auricle is reflected in the pattern of the auricular vectorcardiogram. The horizontal vector loop shows a partial or total deviation posteriorly and a corresponding change of sense of rotation. After commissurotomy, the auricular vectorcardiogram showed, in some of the cases, a pronounced change toward the normal.

It is remarkable that changes similar to those found in patients with severe mitral stenosis have also been observed in a patient with marked left ventricular hypertrophy. The resulting dilatation of the left auricle seems to be responsible for this change of the auricular vectorcardiogram. Possibly the posterior displacement of the auricle by the huge left ventricle also plays a causative role.

In cases of pulmonary heart disease, as well as in cases of pulmonary stenosis, the auricular vector loop is directed anteriorly and prolonged in the caudal direction. This corresponds to the alteration of the partial right auricular vectorcardiogram caused by the dilatation and hypertrophy of the right auricle.

Similar changes have been observed under experimental conditions, when the pulmonary artery has been partially clamped.

In the hearts with ectopic auricular pacemaker, the vectorcardiogram clearly shows the changed conditions of auricular activation, as has been demonstrated in a case of a caudally situated auricular pacemaker.

Conclusions

Vectorcardiography offers the opportunity of clearly demonstrating the altered activation of the auricles under various normal and abnormal conditions. A few examples are presented in this paper.

Summario in Interlingua

Le vectocardiogramma es characteristicamente alterate in multe casos de disordines pathologic del auriculas. Le presente reporto discute alicun exemplos illustrative de iste facto. In casos de stenosis mitral, le alterate vector partial del auricula sinistre es reflectite in le configuration del vectocardiogramma auricular. Le spira vectorial horizontal exhibi un partial o total deviation in direction posterior e un cambiamento correspondente del senso rotational. Post commissurotomia, le vectocardiogramma monstra in alicun casos un pronunciate cambiamento verso le configuration normal.

Il es remarcabile que cambiamentos simile a illos incontrate in patientes con sever stenosis mitral ha etiam essite observate in patientes con pronunciate hypertrophia sinistroventricular. Le resultante dilatation del auricula sinistre pare esser responsabile pro iste alteration del vectocardiogramma auricular. Il es possibile que etiam le displaciamento del

auricula in direction posterior effectuate per le enorme ventriculo sinistre exerce in iste situation un influentia causal.

In casos de morbo cardiac pulmonar e etiam in casos de stenosis pulmonar, le spira vectorial auricular se dirige in direction anterior e es prolongate verso le cauda. Isto corresponde al alteration del partial vectocardiogramma dexteroauricular causate per dilatation e hypertrophia del auricula dextere.

Simile cambiamentos ha essite observate sub conditiones experimental quando le arteria pulmonar es partialmente pinciate.

In cordes con ectopic pacemaker auricular, le vectocardiogramma monstra clarmente le cambiate condition del activation auricular. Isto ha essite demonstrate in un caso de pacemaker auricular situate in le portion caudal del auricula.

REFERENCES

[1] POLZER, K. AND SCHUHFRIED, E.: Ein Beitrag zur Ableitung des Vektorkardiogramms, Wien. med. Wchnschr. **101:** 406, 1951.

[2] PRINZMETAL, M., CORDAY, E., BRILL, I. C., OBLATH, R. W., KRUGER, H. E. AND OTHERS: The Auricular Arrhythmias. Springfield, Charles C Thomas, 1952.

[3] WENGER, R., HOFMANN-CREDNER, D. AND HÖRTNAGL, W.: Über die Reizleitungsverhältnisse in den Vorhofen. Direkte und halbdirekte elektrokardiographische Ableitungen am menschlichen Herzen. I. Mitteilung. Ztschr. Kreislaufforsch. **39:** 653, 1950.

[4] —: Die diagnostische Bedeutung des Oesophagus-Elektrokardiogramms. Wien. Ztschr. f. inn. Med. **28:** 490, 1947.

[5] — AND HOFMANN-CREDNER, D.: Observations on the auricles of the human heart by direct and semidirect electrocardiography. Circulation **5:** 870, 1952.

[6] — AND WICK, E.: Auricular conduction in a case of wandering auricular pacemaker. Am. Heart. J. **49:** 116, 1955.

A Study in Frontal Plane Vectorballistocardiography

By GWENDOLYN L. MORRIS, M.D. AND JOHN R. BRAUNSTEIN, M.D., PH.D.

Frontal plane ballistocardiograms obtained from 10 normal subjects were analyzed and compared with abnormal records obtained from patients with known cardiovascular disease. The normal vector loop is described, and the importance of the transverse ballistocardiogram is discussed. It is suggested that the orientation of the J loop may be related to the anatomic position of the heart. No such relationship was noted with the frontal plane H, I or K vector loops.

ALTHOUGH the human body vibrates in an infinite number of ways, investigators in ballistocardiography have been concerned primarily with motion in the head-to-foot direction. A limited number of investigations have been carried out, for the most part in recent years, concerning other degrees of freedom. Starr and Friedland[1], using a high frequency table, rotated the supine subject about the anteroposterior axis. Nickerson and Curtis[2] did a similar study, using a low frequency, critically damped table. Hamilton, Dow and Remington[3] recorded motion simultaneously in three planes. Scarborough and associates[4] described a method for recording ballistocardiographic vectors, and Franzblau and his group[5] have completed a similar study with a critically damped table. Brandt and associates[6] have also studied the longitudinal, transverse, and sagittal ballistocardiogram by means of a direct body coil and magnetic pickup. Recently, Tannenbaum and his coworkers[7] studied the correlation between cardiac position and the direction of the H, I, J, and K loops. The results of these studies have produced conflicting data in regards to the orientation of the H, I, and J loops. These may be explained by torsional changes, as suggested by Brandt and his associates,[6] or may be the result of various phase relationships, depending upon the type of instrument employed.

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In this study, our purpose was to analyze the frontal plane ballistocardiogram in a series of normal subjects and to compare the results with abnormal records obtained from patients with known cardiovascular disease.

The two-dimensional ballistocardiograph and cathode ray oscillograph used in this study have been described in previous publications.[8, 9] In the time which has elapsed since the instrument was built, circuits have been improved and other modifications have been made for ease of operation. These are described in the Appendix.

MATERIAL

The first group consisted of 10 apparently normal persons. The size and configuration of the heart were normal as determined by chest x-ray films. Twelve-lead electrocardiograms and ballistocardiograms were taken on each subject and these were also normal. The age range of this group was 23 to 38 years. The second group consisted of 10 persons with abnormal ballistocardiograms, eight of whom had known cardiovascular disease. The remaining two subjects were asymptomatic and had normal chest x-ray films and electrocardiograms; one had a labile hypertension, the other subject had a positive nicotine test with a normal basal ballistocardiogram. The ballistocardiogram used in this study was taken 15 minutes after smoking. The age range of the second group was 22 to 70 years.

METHOD

No attempt was made to obtain ballistocardiograms in the basal state, although all subjects rested on the table at least 15 minutes before the records were taken. Photographs of a single complex from the cathode ray tube were taken simultaneously with the longitudinal and transverse ballistocardiogram recorded on the standard paper tape recorders.

The ballistocardiogram recorded on the multichannel oscillograph was marked to identify the

TABLE 1.—*Data Obtained from 10 Normal Subjects*

Subject	Age	Sex	B.P.	QRS axis	Electrical cardiac position	Direction of frontal plane vector ballistocardiogram				
						H loop (headward)	I loop (footward)	J loop (headward)	K loop (footward)	I J loop
1. H. R.	38	F	115/76	+70°	V*	Left	Right	Left	Left	C.c.§
2. J. Z.	31	M	120/76	+50°	SV†	No transverse component	Right	Left	Left	C.c.
3. D. S.	32	M	120/80	+45°	I‡	Left	Right	Left	Left	C.c.
4. R. D.	29	M	115/80	+50°	SV	Right	Left	Left	Left	C.c.
5. J. P.	25	M	125/85	+75°	V	Left	Right	Left	Right	C.c.
6. R. H.	23	M	120/80	+25°	SV	Right	Left	Left	Left	C.c.
7. H. P.	30	M	110/70	+85°	SV	Left	Right	Left	Left	C.c.
8. G. L.	30	F	90/60	+90°	V	Right	Right	Left	Left	C.c.
9. L. H.	24	M	105/70	+65°	SV	Right	Left	Left	Right	C.‖
10. W. R.	27	M	110/70	+60°	SV	Left	Right	Left	Right	C.

* V = vertical.
† SV = semi-vertical.
‡ I = intermediate.
§ counterclockwise.
‖ clockwise.

complex which was photographed. Photographs of the vector loop were obtained during various phases of respiration. The electric position of the heart was determined by the criteria set forth by Wilson and his associates.[10] The hexaxial reference system was employed to determine the QRS axis of the electrocardiogram.

RESULTS

The results obtained from the group of normal subjects are tabulated in table 1, and the ballistocardiograms and vector loops are reproduced in figure 1. The QRS axis of the electrocardiogram indicates a vertical or semivertical position in nine subjects and intermediate position in one. It should be noted that in all subjects, the J loop is directed headward and to the left. The data obtained from the 10 subjects with abnormal ballistocardiograms are reproduced in table 2, and their ballistocardiograms and vector loops are reproduced in figure 2.

DISCUSSION

The results of this study suggest that the orientation of the J loop in the frontal plane of the body may be related to the anatomic position of the heart. However, none of the normal subjects had a horizontal electrical position of the heart. In a previous study,[11] we found no significant correlation between the direction or magnitude of the frontal plane "I J" segment and the rotation of the heart about the anteroposterior axis of the body.

In determining the electrical position of the heart, Tannenbaum and associates[7] used criteria set forth by Wilson.[10] The results of their study demonstrated a complete correlation between the electrical position of the heart and the anatomic position as disclosed by vertical fluoroscopy. In those normal subjects with vertical and semivertical hearts, the J loop was directed headward and predominantly leftward, whereas those individuals with horizontal and semihorizontal hearts had J loops directed headward and predominantly rightward. They also found that the spatial relationships of the H loop and I loop were well correlated with the anatomic position of the heart. In the group of subjects having a vertical or semivertical position of the heart, the H loop was directed headward and leftward or headward and rightward, as compared with individuals who have horizontal and semihorizontal hearts where the H loop is directed headward and rightward. The I loop was directed footward and rightward in the vertical and semivertical group; in contrast, the horizontal and semihorizontal group had I loops directed footward and leftward. The results of our study do not substantiate this relationship.

The transverse component apparently contributes considerably to the abnormal record.

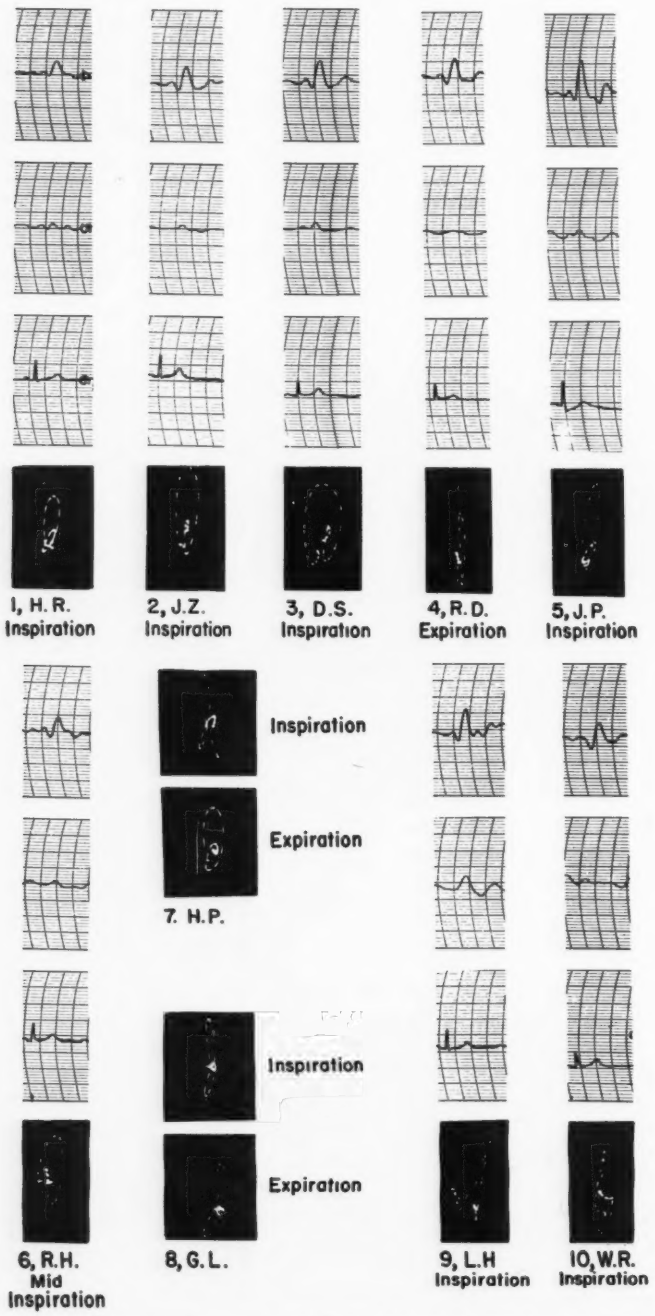


FIG. 1. The above ballistocardiograms were obtained from 10 normal persons. The top tracing is the longitudinal ballistocardiogram. The second record is the transverse ballistocardiogram, and beneath this is lead I of the electrocardiogram. At the bottom is the frontal plane vectorballistocardiogram. These four records were taken simultaneously. The changes in configuration of the vector loops produced by respiration can be seen in the records obtained from subjects 7 and 8.

TABLE 2.—*Data Obtained from 10 Subjects with Abnormal Ballistocardiograms*

Direction of frontal-plane vectorballistocardiogram

TABLE 2.—*Data Obtained from 10 Subjects with Abnormal Ballistocardiograms*

Subject	Age	Sex	B.P.	E.C.G.	Chest x-ray	Diagnosis	Direction of frontal-plane vectorballistocardiogram				
							H loop (headward)	I loop (footward)	J loop (headward)	K loop (footward)	I J loop
1. J. R.	49	M	140/94	Normal	Normal	Essential hypertension	Left	Right	Right	Right	C.c.
2. M. M.	68	F	190/85	Anteroseptal infarct.	Heart size upper limit of normal. Mild elongation and tortuosity of aorta	Myocardial infarction 6 months prior to BCG	Right	Right	Right	Left	C.c.
3. I. H.	70	F	170/78	Anterior infarct.	Mild cardiomegaly	Myocardial infarctions 13 mos. and again 23 days prior to BCG. Diabetes	Right	Right	Left	Left	C.
4. V. H.	60	M	140/80	L.B.B.B. anterior infarction with persistent S-T elevation	Fluoroscopy first revealed ventric. aneurysm 7 years prior to BCG	Massive anterior infarct. 8 years prior to BCG. Ventricular aneurysm	Right	Left	Left	Right	C.c.
5. S. I.	59	M	140/80	Normal	Normal	Angina—10 years	Right	Left	Right	Left	C.c.
6. G. H.	47	F	110/70	Auricular fibrillation, left ventric hypertrophy	Straightening of left heart border, enlarged left auricle, small aortic knob	Rheumatic heart disease. Mitral valvulotomy done 2 years prior to BCG	(H loop not shown on photograph). No transverse component	Right	Left, loops back on itself to right	Right	C.c.
7. M. S.	22	F	114/60	Sinus tachycardia	Normal	Acute rheumatic fever with myocarditis	Right	Left	Right	Left	C.c.
8. D. S.	31	M	128/76	Normal	Normal	Positive nicotine test	Right	Right	Left	Right	C.c.
9. J. E.	35	M	160/90	Frequent ventricular premature contractions	Normal	Essential hypertension	Right	Right	Left	Right	C.
10. W. S.	56	M	106/68	Anterolateral infarct.	Normal	Myocardial infarct. 21 days prior to BCG	No transverse component	Right	Left	Right	C.c.

Even though the wave pattern of the longitudinal ballistocardiogram is normal, the configuration of the frontal plane loop is greatly altered by the amplitude and wave pattern of the transverse component. Vector loops obtained from normal subjects follow the same general pattern and can readily be classified as normal. That is, there is a small headward H

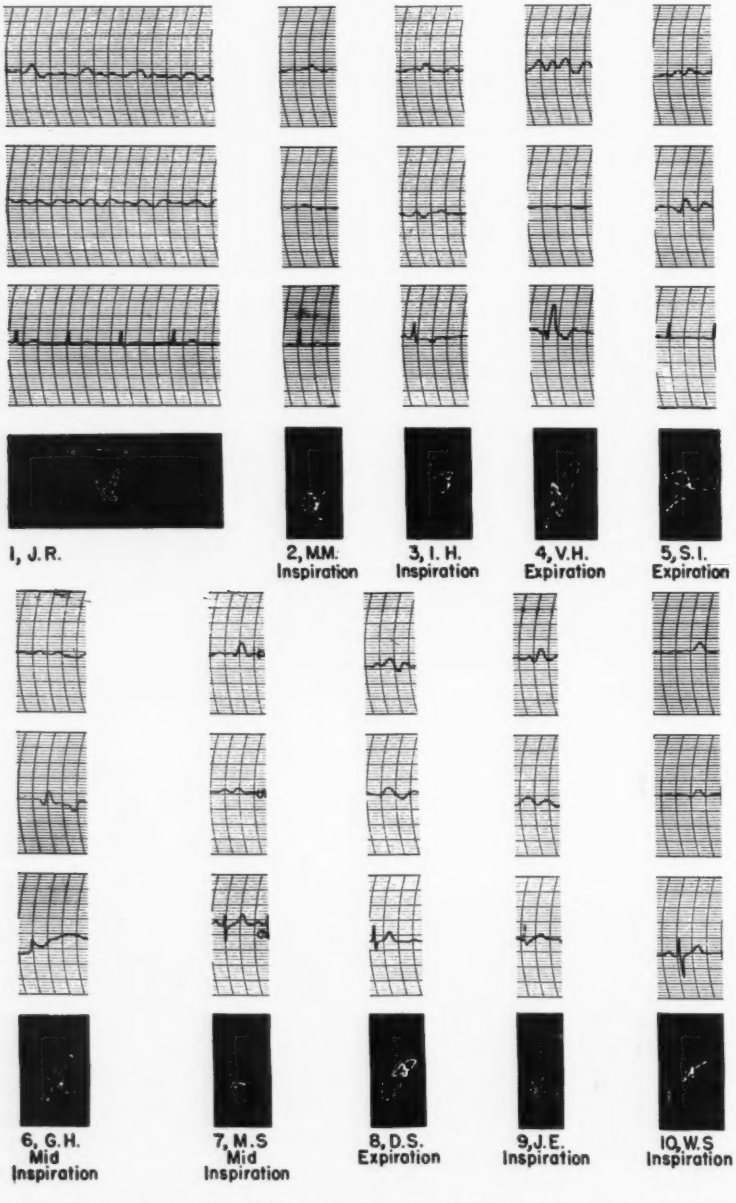


FIG. 2. The 10 records reproduced above are abnormal. Subjects 1 through 7 and subject 10 have known cardiovascular disease. Subject 8 has a positive nicotine test, and subject 9 has a labile hypertension. The tracings are in the same order as in figure 1.

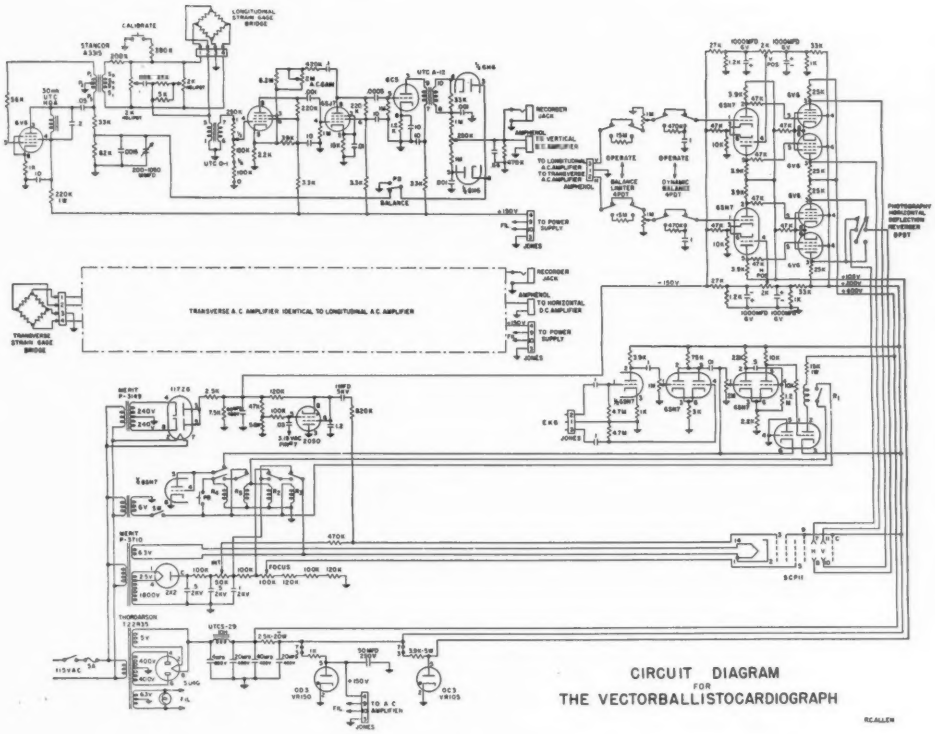


FIG. 3

wave, followed by a narrow footward I loop. The largest loop is the headward J loop, which generally does not have much of a transverse component and is at least twice as high as it is wide. The vector loops obtained from patients with known cardiovascular disease generally have a conspicuous transverse component. The H loop may be tall and wide, and the I loop shallow and with a more transverse component than the normal. Usually, the J wave is of low amplitude with a transverse component which is almost as large or larger than the longitudinal component. The direction of the J loop may change from its initial clockwise rotation to counterclockwise or alter direction from counterclockwise to clockwise. It is possible that torsional changes produced by the heart beat may play an important role in determining the direction of rotation of the various vector loops. We are engaged in a study at the present time to evaluate the effects of torsion on the ballistocardiogram.

SUMMARY

1. The normal frontal plane ballistocardiogram is described.

2. The 10 normal subjects had J loops directed headward and to the left. The H loop was directed headward and rightward or leftward, and the I loop was directed footward and leftward or rightward. All of these subjects had vertical or semivertical hearts.

3. The transverse component appears to be of little significance in the normal frontal plane ballistocardiogram.

4. Vector loops obtained from patients with known cardiovascular disease generally have a conspicuous transverse component, often exceeding the magnitude of the longitudinal component.

5. In the abnormal record, the direction of

the J loop may change from its initial clockwise rotation to counterclockwise, or alter direction from counterclockwise to clockwise. This was not observed in the normal records.

Summario in Interlingua

1. Es describite le normal ballistocardiogramma a plano frontal.

2. Le 10 normal subjectos includite in le studio habeva spiras J a orientation verso le capite e verso le sinistra. Le spira H esseva orientate verso le capite e verso le dextera o le sinistra. Le spira I esseva orientate verso le pedes e verso le sinistra o le dextera. Omne iste subjectos habeva cordes vertical o semivertical.

3. Le componente transverse es apparentemente de pauc signification in le normal ballistocardiogramma a plano frontal.

4. Spiras vectorial obtenite ab patientes con cognoscite morbo cardiovascular ha generalmente un conspicue componente transverse que frequentemente excede le magnitude del componente longitudinal.

5. In le registration anormal, le rotation del spira J pote cambiar su direction initial ab dextrorse a sinistrorse o ab sinistrorse a dextrorse. Iste phenomeno non esseva observate in registrationes normal.

REFERENCES

[1] Starr, I. and Friedland, C. K.: On the cause of the respiratory variation of the ballistocardiogram, with a note on sinus arrhythmia. J. Clin. Invest. **25:** 23, 1946.

[2] Nickerson, J. L. and Curtis, H. J.: The design of the ballistocardiograph. Am. J. Physiol. **142:** 1, 1944.

[3] Hamilton, W. F., Dow, P. and Remington, J. W.: The relationship between the cardiac ejection curve and the ballistocardiograph forces. Am. J. Physiol. **144:** 557, 1945.

[4] Scarborough, W. R., Beser, J., Talbot, S. A., Mason, R. E., Singewald, M. L. and Baker, B. M., Jr.: A method for recording ballistocardiograph vectors. Bull. Johns Hopkins Hosp. **87:** 235, 1950.

[5] Franzblau, S. A., Best, W. R., Guillemia, V. Jr. and Marbarger, J. P.: Three dimensional vector ballistocardiography. J. Lab. & Clin. Med. **36:** 824, 1950.

[6] Brandt, J. L., Caceese, A., Dock, W. and Schrager, A.: The motion of the thorax during the heart cycle: A comparison of longitudinal, lateral and dorso-ventral ballistocardiograms. J. Clin. Invest. **30:** 971, 1951.

[7] Tannenbaum, O., Vesell, H. and Schack, J. A.: The spatial vectorballistocardiogram. Am. Heart J. **48:** 562, 1954.

[8] Braunstein, J. R., Oelker, C. E. and Gowdy, R. C.: Design of a two-dimensional ballistocardiograph. J. Clin. Invest. **29:** 1219, 1950.

[9] —: The ballistocardiogram, a dynamic record of the heart beat. Springfield, Charles C Thomas, 1953.

[10] Wilson, F. N., Johnson, F. D., Rosenbaum, F. F., Erlanger, H., Rossman, C. E., Hecht, H., Cotrim, N., Menzes de Oliveira, R., Scarsi, R. and Baker, P. S.: The precordial electrocardiogram. Am. Heart J. **27:** 19, 1944.

[11] Morris, G. L. and Braunstein, J. R.: A two-dimensional ballistocardiographic study of 59 apparently normal subjects. An analysis of the IJ segment as it relates to body surface area and the anatomic position of the heart. Circulation **11:** 767, 1955.

Appendix

The head-to-foot component is placed on the vertical deflection plates of the cathode ray oscilloscope and the side-to-side component is placed on the horizontal deflection plates. The following features have been added to the revised instrument:

(a) *Provision For Making Simultaneous Paper Tape Records*

The longitudinal and transverse voltages from the strain gage amplifiers have been made available for insertion into standard paper tape recorders for permanent and simultaneous records.

(b) *Direction Indicator and Timer*

To facilitate quantitative study of complex photographs, the scope tube beam is modulated by a saw tooth wave form, so that the pattern on the scope face is made up of a series of arrowheads which indicate the direction in which the complex is traced. Timing is accomplished by synchronizing the saw tooth generator with the 60 cps line voltage. The arrowheads occur at intervals of one sixtieth second.

(c) *Horizontal Deflection Reverser for Photographic Presentation*

The camera used to record the single complex reverses the transverse component. In order to have the photographs appear in the normal fashion, the reflection reversing switch was placed in this channel.

A schematic diagram of the circuit for the ballistovectorscope is shown in figure 3.

CLINICAL CONFERENCE

Editor: EDGAR V. ALLEN, M.D.

Associate Editor: RAYMOND D. PRUITT, M.D.

Presentation of a Case for Diagnosis

A Clinicopathologic Conference

This conference was presented at the Fourth Annual Heart Symposium sponsored by the Indiana Heart Foundation at the Indiana University School of Medicine, Indianapolis, Ind. on Jan. 20, 1955. Participating were members of the Research Committee of the American Heart Association and members of the Faculty of the School of Medicine. Participants from the Research Committee were: Dr. Robert H. Bayley of the University of Oklahoma College of Medicine, Oklahoma City; Dr. Howard Burchell, Mayo Clinic, Rochester; Dr. Howard Sprague, Harvard Medical School, Boston. Participants from the Indiana University School of Medicine Faculty were: Dr. James O. Ritchey, Department of Medicine, Moderator; Dr. Warren Coggeshall, Department of Medicine; Dr. John A. Campbell, Department of Radiology; Dr. Edward Smith, Department of Pathology; Edited by: Dr. Roy H. Behnke, Department of Medicine.

CASE HISTORY

THE PATIENT, a 45 year-old white female, was admitted to the Robert W. Long Hospital of Indiana University Medical Center on March 29, 1954 with the complaints of fatigue and shortness of breath. Past history, as related by the patient, revealed that she had experienced exertional dypsnea and cyanosis after exercise for an indefinite period antedating her enrollment in grade school. She denied squatting to relieve the dyspnea. At the age of 11 she was told that she had heart disease and during the succeeding years she led what she described as a "restricted" existence.

For seven years prior to her admission the patient had worked in a factory where she was able to perform her duties which required that she stand eight hours each day, but did not necessitate heavy lifting or walking. During the last two years she had been aware of a definite progressive increase in exertional dyspnea and the degree of apparent cyanosis. Symptoms of frank congestive heart failure, cough, paroxysmal nocturnal dyspnea and ankle edema, developed in December of 1953. She was then placed upon digitalis, mercurial diuretics and a salt restricted diet.

Physical Examination: The patient was a well developed, well nourished woman with moderate generalized cyanosis. The neck vessels were not distended. Blood pressure was 122/88, pulse 72 and regular. The point of maximal impulse was not located. One observer felt a faint systolic thrill in the pulmonic area. No precordial shock was felt. Auscultation disclosed an accentuated second sound at the cardiac apex. A grade II blowing systolic murmur was heard along the entire left sternal border, but with greatest intensity in the third left interspace. The second pulmonic sound was accentuated and louder than the aortic second sound. No murmurs were heard at the base.

Laboratory Findings: Urine analysis and blood serologic tests for syphilis were negative. Hemoglobin was 16.4 Gm. Red blood cell count was 5,640,000; white blood cell count was 8,500 with a normal differential.

Hospital Course: On April 8, 1954, the patient was taken to surgery. Her postoperative course was stormy and death occurred on April 10, 1955. An autopsy was then performed.

DR. J. A. CAMPBELL: On cardiac fluoroscopy generalized enlargement was seen in the frontal plane which, upon rotation, was found to be chiefly due to the dilatation in the area of the left ventricle. The right atrium and other border-forming cardiac structures were not remarkable. No calcification was seen in the pericardium, in the musculature, or in the region of the valves or larger peripheral vascular structures. The lungs were clear and the pulmonary

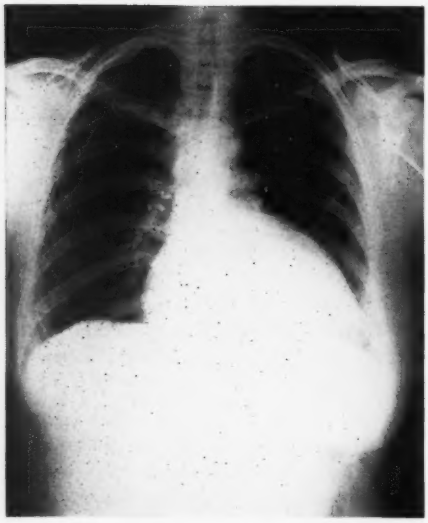


FIG. 1. Posteranterior chest film.

vasculature was felt to be more difficult to define than normal.

In the frontal view (fig. 1) the left inferior cardiac segment is somewhat elevated and high with respect to the diaphragm, and this was taken to reflect left ventricular change in the way of dilatation. The aortic knuckle was normal. The aorta descended on the left in normal relationship to the barium filled esophagus. The vena caval borders were straight and full, but not excessively so. The right atrial border was satisfactory. The pulmonary arteries were somewhat smaller than normally expected, and the peripheral lung fields were considerably more clear than usual in a 45 year-old woman with cardiac dimensions of this magnitude. On the lateral projection (fig. 2) there is an increase in the anteroposterior dimension of the heart. It assumes a somewhat spherical globular configuration with the left ventricular contour making sharp impression on the esophagus but not excessively penetrating the posterior cardiac space. The frontal heart is tight against the sternum so that one might conceive of some right ventricular dilatation as well. There is no left atrial impression of significance and the aorta is within normal limits with no apparent calcification.

In the right anterior oblique projection (fig. 3) there is no suggestion of left atrial dilatation. Again the overall increase is primarily attributable to right ventricular enlargement. In the left anterior oblique (fig. 4) there is considerable prominence of the left ventricular segment and the right ventricular border also is prominent. The pulmonary artery is small.

DR. W. E. COGGESHALL: This patient was sent for catheterization on March 31, 1954 (fig. 5) because it was felt that she had a considerable right-to-left intracardiac shunt because of her cyanosis. The catheter entered the superior vena cava where saturation was 38 per cent and the pressure was found to be 3.2 mm. Hg, which is a mean pressure. The right atrial pressure was 7.5 mm. Hg, somewhat higher than is normally found. The right atrial saturation was 46 per cent. In the right ventricle we found pressure of 14/3 mm. Hg and a saturation of 47 per cent. In the right pulmonary artery, the pres-

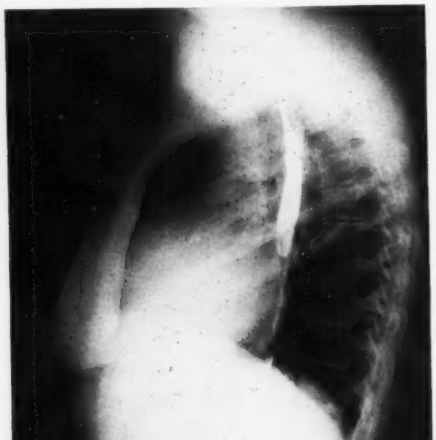


FIG. 2. Left lateral chest film.

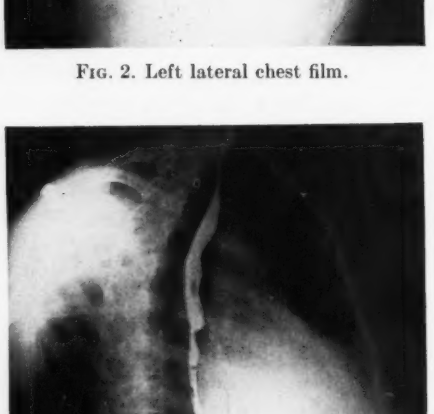


FIG. 3. Right anterior oblique chest film.

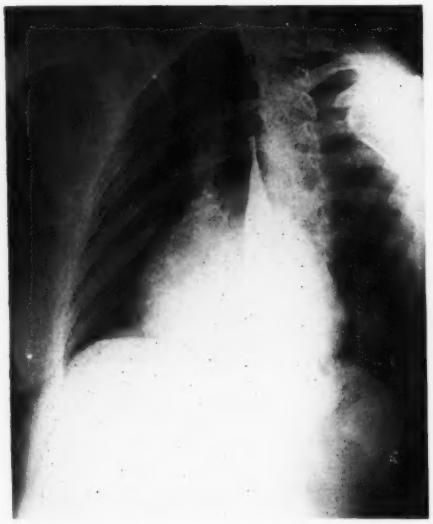


FIG. 4. Left anterior oblique chest film.

sure was found to be 17/4 with 44 per cent blood oxygen saturation.

Arterial study showed the following: blood pressure was 91/62 and the blood oxygen saturation was 68 per cent without oxygen. With five minutes of 100 per cent oxygen, arterial blood oxygen saturation rose to 78 per cent, still markedly unsaturated. At this time we felt confident the shunt was not from the pulmonary system into the aorta because of the marked difference in pressure between the lesser circuit and systemic circuit. The pressure relationships were such that a shunt at the ventricular level was thought improbable, so we felt that if a shunt were present it was at the atrial level. We did not traverse a defect in the atrium during this procedure and we could not enter the inferior vena cava.

Following that catheterization we felt that the inferior vena cava might be displaced and/or we might have a large common atrium. It was decided that the patient should have an angiocardiogram by means of a catheter in the inferior vena cava. Prior to doing the angiocardiogram, we decided to investigate the inferior vena cava and make sure that it emptied into the right atrium. The following findings were noted as we continued with the catheterization (fig. 6). Again, we found the right atrial mean pressure to be elevated—the saturations remained approximately the same. At that time we were able to enter the left atrium and a pulmonary vein where we found normal saturations. We found the right atrial pressure to be higher than the left, a relationship which is the reverse of normal (fig. 7). At that time the catheter also went into the left ventricle where we found a mild increase in saturation when compared to the saturation in the left atrium. This would be compatible with a venous shunt at the atrial level combining with the oxygenated blood coming from the pulmonary veins. At that time we felt that we had established that there was a shunt through the atrial septum. We were not positive why the pressure was elevated in the right atrium. The right atrial pressure was ex-

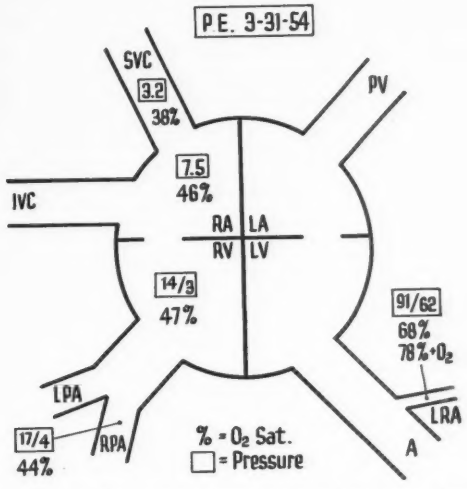


FIG. 5. Cardiac catheterization data from first procedure done via the superior vena cava, March 31, 1954.

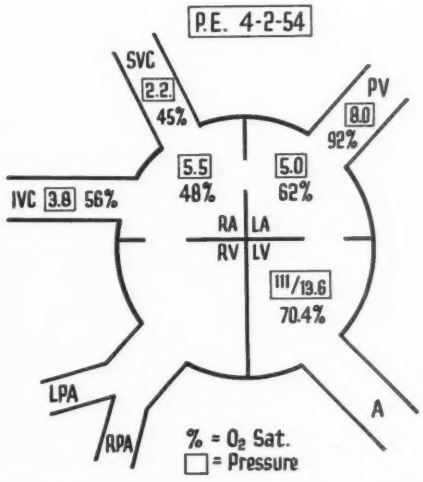


FIG. 6. Cardiac catheterization data from the second procedure done via the inferior vena cava, April 4, 1954. The catheter did pass into the left heart through the atrial wall.

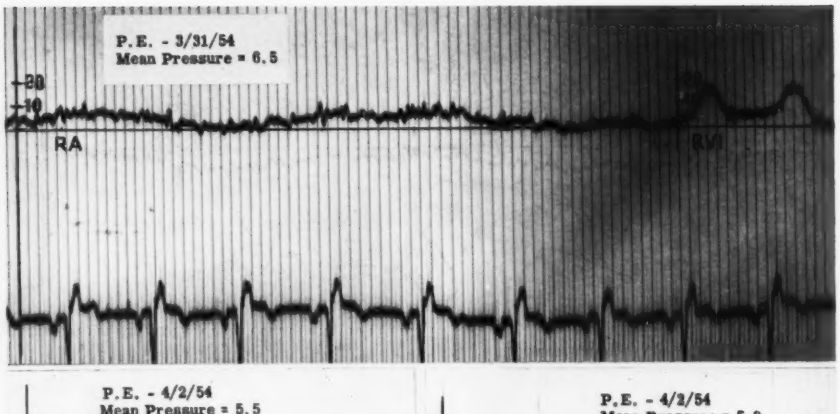


FIG. 7. Atrial pressure records.

amined closely for a pressure pattern suggestive of tricuspid insufficiency, but none was found.

DISCUSSION

DR. H. SPRAGUE: May I ask one question even though the answer seems to be implicit in this history? Was the patient operated upon for her heart abnormality?

DR. J. O. RITCHEY: You have the answer to this, Dr. Close?

DR. W. D. CLOSE: Yes.

DR. H. SPRAGUE: The reason I asked this of my friend is that it permits me to offer a few insulting remarks. If I were not unhappy about this case, you would not have any fun at all. I assure you I was very disturbed about this situation. I must say at once that I had recourse to our competent catheter team and especially Dr. Allan Friedlich to see what they thought might be the possible interpretation of these figures. As I intend to go ahead and stick my neck out and make a diagnosis I will have to assume a few things and issue the following insults. (1) If my diagnosis is correct, the patient probably should not have been catheterized. (2) Since the patient was catheterized, I must say that either the catheter figures are wrong or they were misinterpreted; otherwise the patient would not have been operated upon for the lesion, which I think this patient had, has been considered inoperable.

Now you see these are all assumptions. Let us review the history a moment. The patient had fatigue, dyspnea and cyanosis for as long as she could remember, especially exertional dyspnea and cyanosis even before she went to school. There is no statement as to whether she was a "blue baby" or not. She denies squatting. That is included because, if the patient did not squat, one may assume that this is probably not a case of Fallot's tetralogy. That is not completely accurate, of course. At the age of 11 she was told she had heart disease; therefore, we know that something went wrong a long way back and we assume that the cardiac condition was something with which this child was born

She led a restricted existence but did rather well; she was working and she was 45 years old.

For seven years prior to her admission she had worked in a factory and was able to keep on with her job and stand for eight hours a day. There was no heavy lifting or walking connected with her work, but she became more and more short of breath when she exerted herself; the cyanosis got worse, and finally she went into congestive failure.

I would judge that the physical examination did show moderate cyanosis. I understand that there was no clubbing of the fingers or toes; neck vessels were not enlarged and not dilated or pulsating. The blood pressure was normal. There might have been a faint thrill in the pulmonic area where she had an accentuated second sound louder than the aortic second sound. We frequently find difficulty in correlating accentuation of pulmonic second sound with catheter evidence of pulmonary hypertension, which this person did not have. There was a grade II systolic murmur along the left sternal border and no murmurs at the base. She did have a high hemoglobin and a red blood cell count of 5.6 million and right bundle branch block in the electrocardiogram.

The cardiac fluoroscopy, which you have described, may I say very cautiously—showed enlargement in the region of the left ventricle, right ventricle, and left atrium. For example, when you get right bundle branch block and a heart which, when looked at sideways is tight against the anterior chest wall, you can be sure that there is a big right ventricle; and as you know the radiologists often sneak into the electrocardiographic laboratory and look at the electrocardiogram before they say whether the right or left ventricle is enlarged. It is conceivable that we are dealing with a big right-sided heart here that is just pushing the left side of the heart back and to the left. The striking thing is that the arterial trunks are small, as evidence here of decreased pulmonary flow rather than increased pulmonary flow.

The catheter data will, no doubt, be further discussed later. As the catheter passes into the right atrium from the vena cava, we apparently find more oxygen in the blood which must come through the interatrial septum, or by anomalous position of the pulmonary venous drainage into the right atrium, or conceivably retrograde in some particular fashion; but it would have to be a rather peculiar fashion. We find, as we go along into the right ventricle, no hypertension of that chamber and further no hypertension in the pulmonary artery. When we get the figures for oxygen saturation, we wonder where in the right side of the heart the end of this catheter actually was. Well, as our catheter friend has said, there seems to be an interatrial septal defect. If that is so, why isn't there evidence of an increase in pulmonary circulation? There doesn't seem to be any evidence of an interventricular communication for the only increase in oxygen of significance occurs there in the right atrium. It doesn't seem to make sense for a pulmonary stenosis. There is certainly no right ventricular hypertension; there is no poststenotic dilatation of pulmonary artery; for example, and no great difference in pressure gradient across the pulmonary valve. It doesn't seem to make very good sense for a tetralogy of Fallot. Sticking my neck out, as I say, it does make sense for one condition—a situation which I myself have never diagnosed during life; which indeed, was said to be impossible of diagnosis some years ago. However, when Dr. Paul Wood came over from London two or three years ago, he said it is an easy bedside diagnosis in children, and the only patients I have seen with it were children. As all of you now know, since you probably have made the diagnosis already, this is presumably "Ebstein's disease" or "anomaly" of the tricuspid valve.

There is a big right-sided heart consistent with Ebstein's disease. In this condition the tricuspid valve is displaced downward into the right ventricle with a very small functioning right ventricle beyond the tricuspid valve and a great big dilated thin-walled part of the right ventricle proximally, communicating directly with the right atrium. It is characterized by cyanosis which usually appears at birth and then disappears, only to reappear later as the prolonged malfunction of this abnormal tricuspid valve results in increased back pressure blowing open the foramen ovale. The foramen may increase in size over the years to the point

where it becomes a large defect. The decrease in the flow to the lungs is explained by poor forward output of the right ventricle. These catheter findings seem to me, at least, to be consistent with what is going on in this big chamber composed of the right atrium and the upper part of the right ventricle.

The reason that I had for some of these insults I mentioned was that if it was assumed that this was a case of Ebstein's disease, catheterization might be considered to be dangerous because arrhythmias can be initiated easily by catheterization in this condition and the catheter might get tangled in this rather complicated, deformed, tricuspid valve. Certainly there is supposedly some danger of perforation of the thin chamber.

According to Taussig's group (I have not had a chance to look through the literature) one patient has been known to live to the age of 61 and one to 60 years, but the average age at death is 24 years. So far as I know, this entity has not been diagnosed definitely during life, although one case, three years ago and two cases two years ago, were supposed to have been diagnosed, two by catheter and one by angiocardiogram. I can not offer a diagnosis that seems to me better than Ebstein's anomaly and if I am wrong, I will go down smiling; but if I am wrong I really think I should turn in my badge and gun.

Dr. R. H. Bayley: I would like to take a peek at that electrocardiogram (fig. 8). Right bundle branch block in congenital heart disease often offers us additional information, over and above what we see in a more normal electrocardiogram. In uncomplicated right bundle branch block we look for a double R wave, two R deflections on the right side of the precordium. The first of these two R deflections is written by the electromotive forces passing through the septum from the left side only. Following this is a negative deflection which is written by the electromotive forces in the free wall of the left ventricle. For example, when there is a left ventricular hypertrophy, we expect this cleft to be rather prominent. And finally, the right ventricle which is activated last in right bundle

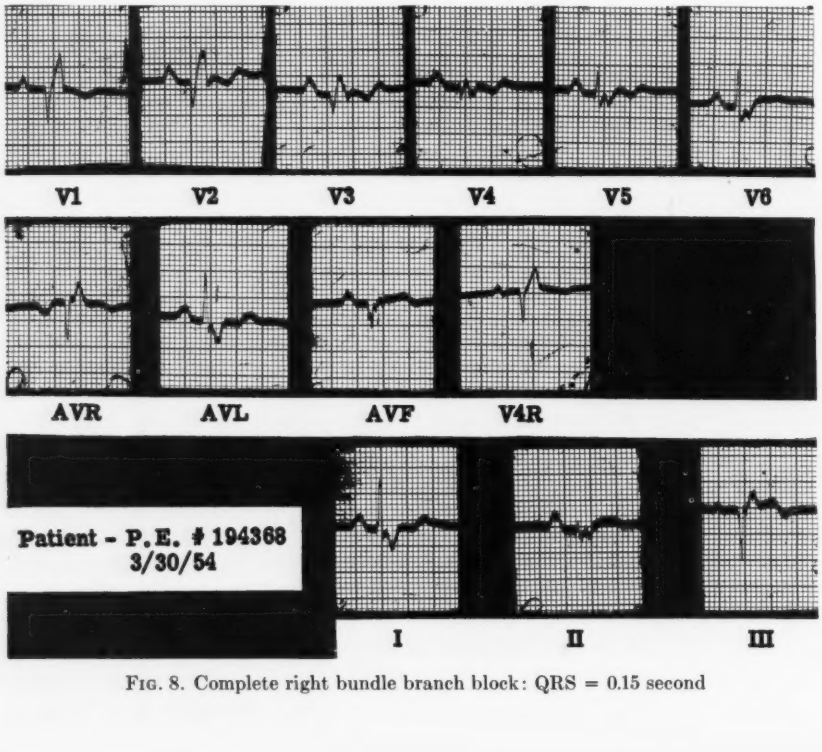


Fig. 8. Complete right bundle branch block: QRS = 0.15 second

branch block is responsible for the final R deflection. So in a sense, we have a separation of the deflections written by the two ventricles in right bundle branch block. If there is a large hole in the septum, or if that septum has been infarcted in the presence of right bundle branch block, the first R deflection disappears. The first R deflection in the first two precordial leads of this patient's curve is missing. However, the second R deflection here is quite broad and prominent; we might surmise that this could be an instance of right ventricular hypertrophy. I would be much less sure of the septal defect than of right ventricular hypertrophy.

On the left side of the precordium we can interpret the initial ventricular deflections equally satisfactorily when right bundle branch block is present or when it is absent. In other words, if left ventricular hypertrophy is present here, we would expect those deflections to be rather prominent and actually they are quite small. So, I think the electrocardiogram is very much in favor of right but not left ventricular hypertrophy and we still have to explain the absence of the initial R deflection which is ordinarily written by the septum.

We have seen a case in which there was a marked hypertrophy of the right ventricle but the right ventricle was not very large. It was a very thick-walled, small chamber, and the tricuspid valve was in essentially normal position. There was, in effect, a very small cavity in the right ventricle and we obtained pressure distributions in that particular case which were entirely similar to the pressure findings presented today. An auricular septal defect was also present. There was this difference clinically; our patient was in his thirties, he was considerably more cyanotic than this patient and he had been cyanotic from birth. Except for the grade of cyanosis, this picture would fit with that of a markedly hypertrophied small right ventricle with atrial septal defect, not necessarily Ebstein's disease.

Dr. H. Burchell: I think that this patient does have Ebstein's disease. I am going to borrow a sentence from my friend, Dr. Frances Wood. If this patient does not have Ebstein's disease, then Dr. Ritchey did the post-mortem on the wrong patient. I think that these particular findings present a clinical picture which allows a specific clinical diagnosis: These findings are an atypical type of right bundle branch block, a peculiar shaped heart with very poor vascular markings in the lungs and then a picture of heart failure and/or cyanosis in the second or third decade of life. Some patients have a characteristic double murmur in the pulmonary area which may be timed by the phonocardiogram as being related to auricular and ventricular systole. Dr. Paul Wood has said that it is dangerous to catheterize these patients, but I do not believe this is so. In some patients we have not catheterized, the clinical diagnosis was enough, but we have felt in the other cases that it would be well to know the hemodynamic alterations that were present, because there is considerable variation in Ebstein's deformity from heart to heart.

The deformity mainly relates to one part of the tricuspid valve which may be a very long veil-like arrangement which may be displaced markedly toward the outlet side of the ventricle. The right ventricle may actually be a pouch, so if you cut across it you might see two chambers separated by this veil-like structure somewhat similar to the tricuspid valve arrangement in the heart of birds. Some of these valves are competent and some are incompetent. I think Dr. Taussig has pointed out that the right ventricular failure is related to the inadequate size of the right ventricle; however, I would like to point out that there is more of a variation than that. Sometimes there is perhaps a true right ventricular stenosis from the point of view of the inadequate size of the right ventricular chamber. Sometimes the chamber is inadequate and sometimes the tricuspid valve is incompetent and sometimes it is not. In this case, the mean pressure in the right atrium could be apparently increased over the inferior and superior vena cava for two possible reasons: you might have a tricuspid pulse in the right atrium which caused an error in the calculation of the mean pressure or the catheter might have been a little bit further along and part way into this unusual, right-sided chamber.

We have seen one patient who had postural dyspnea, marked effort dyspnea and cyanosis. We studied him over a period of 18 months and

this symptom-pattern was constant and his arterial saturation on exercise, or sometimes just standing, dropped to levels below 50 per cent. After considerable thought we said this man would be better off with his foramen ovale closed. One can predict that the interatrial communication is likely to be the result of a patent foramen ovale, rather than a large atrial septal defect. This patient was operated upon, had an uneventful recovery and has been normally active for two years. He was a rabbit hunter and he is now able to go back doing that. However, this is regarded as a palliative procedure. We have restored this man to well being for a period of two years, but it is expected that eventually the heart will fail. In another individual, a 35 year old sheet metal worker who has been getting along quite well, we have not recommended any surgical procedure. One patient who came to us in congestive heart failure was observed intermittently for two years before his death. Our total experience would indicate that perhaps in certain individuals without heart failure, where hypoxia plays a significant role in symptoms, one might advise surgical closure of the atrial septum. We operated upon one child two months ago who had fainting attacks. The operation was successful in that the arterial oxygen saturation came up to normal with closure of the atrial defect. The child died, not recovering consciousness after surgery; there was cerebral infarction probably from an embolus. Children or adults with this disease must be regarded as very high surgical risks, but there is a possibility that there may be a small number of them who present primarily a hypoxic picture who could be given surgical palliation.

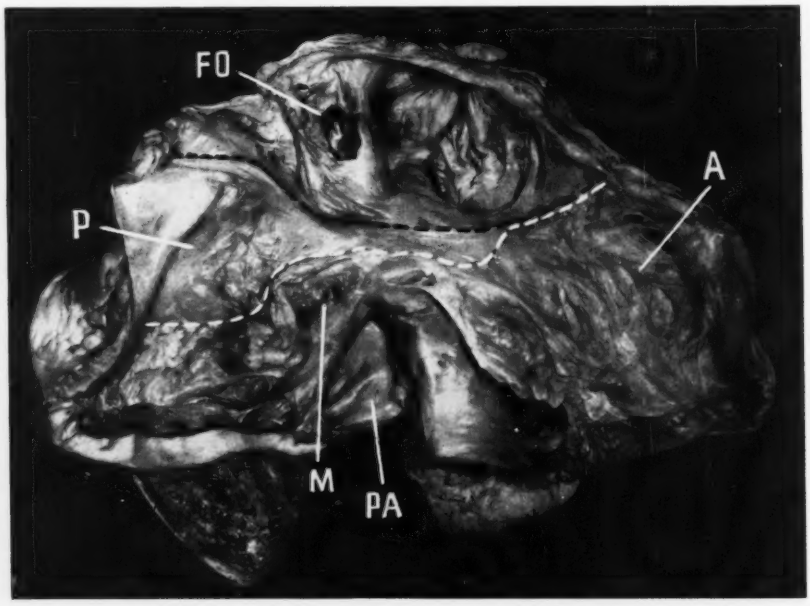


FIG. 9. (Autopsy No. 7057).: Ebstein's malformation of the tricuspid valve and a patent foramen ovale. An interior view of the right atrium and ventricle is shown. The black line indicates the expected normal line of attachment of the tricuspid valve. The white line indicates the actual line of attachment of the tricuspid valve in this case. The size of the atrium above the white line is increased at the expense of the size of the ventricle below. Note also the partial attachment and irregularity of the posterior leaflet (*P*) and the anterior leaflet (*A*), both of which are fenestrated. The medial leaflet (*M*) is short enough to suggest that an insufficiency of that leaflet may have existed. The foramen ovale (*FO*) is patent and measures 15 by 20 mm. The pulmonary conus, valve and artery (*PA*) are essentially normal. The left atrium, left ventricle and associated structures are normal except for the patent foramen ovale.

DR. E. B. SMITH: May I summarize the clinical problem as it pertains to the pathologic findings? The patient was cyanotic, had an increased pressure in the right atrium and a route for the shunt of blood from the right to the left side of the heart. Ebstein's malformation has been *correctly* proposed to explain the clinical and laboratory findings. The lesion of the heart is described in the legend to figure 9.

At the time of the postmortem examination the foramen ovale was closed by silk sutures which had been placed there two days before death. Dr. Harris B. Shumacker had invaginated the anterolateral wall of the right atrium across the base of the right auricular appendage. He had then neatly sutured the invaginated wall to the margins of the foramen ovale to cover it completely. The sutures were in place and the foramen was still occluded at death.

In order to prepare an informative photograph, the sutures were removed from the specimen postmortem. The heart weighed 455 Gm. The right ventricular wall was three mm. in thickness and the wall of the left ventricle was 12 mm. in thickness. The circumference of each of the valvular rings was as follows: tricuspid, 18 cm.; pulmonic, 8.5 cm.; mitral, 11.5 cm.; aortic, 8 cm. The weight of the lungs totaled 720 Gm. The postmortem examination was limited to dissection of the thorax. According to our records there was a "tendency to clubbing" of the fingers of this woman. Except for the lesion of the heart, no congenital abnormalities were observed.

This is a rare congenital anomaly of the tricuspid valve, first described by Ebstein in 1866. Less than 30 cases have been reported. In most instances the foramen ovale is patent. The clinical diagnosis is difficult and has rarely been made. I congratulate Dr. Sprague upon his correct diagnosis.

CLINICAL PROGRESS

Editor: HERRMAN L. BLUMGART, M.D.

Associate Editor: A. STONE FREEDBERG, M.D.

The Neurogenic Control of the Blood Vessels

By SIMON RODBARD, M.D., PH.D. AND LOUIS N. KATZ, M.D.

FOR THE last three decades our associates and we have been concerned with the study of the control of the blood vessels and on occasion have reviewed special aspects of the subject.[1-5] In the present report we wish to concentrate on neurohumoral aspects of the control of the vessels, dealing with the recent literature and some of our recent work on the cranial and pulmonary vasculature.

THE NEED FOR REGULATION

If all the vascular beds of the body were to open simultaneously to their full capacities, the total peripheral resistance would disappear and the cardiac output would be swallowed up, leaving no trace of an arterial pressure. In order, therefore, to permit the circulatory pumps and vessels to carry out their proper functions, most of the blood vessels of the body must be partially or even severely constricted a great deal of the time. To accomplish this, vasoconstriction must be balanced neatly against vasodilatation, with both attuned to cardiac output and to tissue needs.

The control of the degree of *vasodilation* of the blood vessels is achieved primarily by the interplay of peripheral mechanisms. These include the effects of metabolic vasodilators, produced by muscles and other working tissues, which act directly or through axone reflexes. These local mechanisms are supplemented by a system of efferent vasodilator nerves transmitting messages from the central nervous system.[6] When these vasodilator influences are unchecked, a state of vascular collapse and shock may ensue.

Against these tendencies, a group of powerful *vasoconstrictor* mechanisms is available and in constant function. Their role is to reduce unnecessary blood supply to tissues. This vasoconstriction is guided by a hierarchy whereby certain favored organs ensure their own blood supply, particularly the brain, the heart and the kidney. The control of the degree and sites of vasoconstriction, depends predominantly on the action of the central nervous system and the influence of hormonal action including the permissive effects of the steroids and other substances. The relative distribution of the cardiac output to the various organs is influenced by the vasomotor center of the medulla oblongata, which responds to impulses from all the tissues of the body, including the other portions of the brain itself. This center therefore ultimately sets the appropriate level of systemic blood pressure. This control can best be illustrated by considering some of the driving forces of vascular regulation.

REGULATION OF THE CEREBRAL BLOOD SUPPLY

At the turn of the century Cushing[7] showed that intracranial compression, by impeding blood flow to the brain and producing "ischemia", brought about a rise in blood pressure sufficient to balance the compressing force, thereby ensuring delivery of blood to the collapsed cerebral vessels. Recent work has

From the Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago, Illinois.

The Cardiovascular Department is aided in part by the Michael Reese Research Foundation and this study was supported in part by the United States Air Force under Contract No. AF 18 (600)-884, monitored by the Arctic Aeromedical Laboratory, Ladd Air Force Base, Alaska, APO 731, Seattle, Wash.

demonstrated that this pressor response is dependent on pressure receptors rather than to oxygen hunger.[8] Thus, in experiments in which the intracranial pressure was raised acutely to high levels for only a second or two (a period probably too short for the development of significant ischemia) the magnitude of the pressor response was proportional to the degree of compression. Graded responses in blood pressure were obtained by momentary compressions of 150, 200 or 250 mm. Hg, all higher than the blood pressure level.

These experiments have led to the concept that a pressure-sensitive receptor, similar in its behavior to the carotid sinus[9] is present in the cranial cavity.[10, 11] A receptor in the cranium would differ, however, by responding to the *difference* in pressures between the distending pressure inside the artery and that produced by the compression. In such baroceptors a rise in intracranial pressure would have the same effect as an equal fall in intra-arterial pressure, and thereby initiate mechanisms to maintain the blood pressures at levels satisfactory for cerebral perfusion.

Pressor Mechanisms Initiated by Intracranial Compression

Some of the mechanisms whereby blood pressure regulation is achieved can be illustrated by the response to graded compression of the brain. In animal experiments an acute increase in intracranial pressure initiates a threefold response in the regulating mechanisms. A direct neurogenic vasoconstriction occurs within a second or so after the onset of the stimulus; this effect tends to level off within about 10 seconds. Evidence has accumulated to show that at the time of this initial vasoconstriction, a graded amount of a pressor material is released into the venous blood stream. After the time required for a full transit of the circulation, the blood-borne pressor material arrives at the arterioles and the second pressor effect becomes manifest. Blocking experiments utilizing tetraethylammonium, benzodioxane and dibenamine have indicated that the pressor material released into the blood stream is probably* norepinephrine.[10] A third pressor mechanism, apparently resulting from venoconstriction and mobilization of blood reservoirs, increases the circulating blood volume.[11] These experiments illustrate how a variety of discrete mechanisms may act in concert to provide a quantitative response to a neurogenically determined pressure-regulating stimulus. Similar relationships are being established for other organs which play a role in this regulation.

Hypothalamic Mechanisms

The important role of the hypothalamic centers in blood pressure regulation has become apparent as a result of recent studies on hypothermia,[12-14] which demonstrate that the blood pressure level is influenced by body temperature. When the body temperature decreases from the normal 37 C. to 25 C., the blood pressure may descend from a mean of 100 mm. Hg to 60 mm. Hg. Thus, a blood pressure which is "normal" at one body temperature may be an "abnormal" pressure at a lower temperature. Concomitant with these temperature-induced blood pressure changes, reductions occur in the circulating blood volume,[15] in the cardiac output and in oxygen requirements.[16]

Failure to appreciate the temperature-pressure relationship led early workers in clinical hypothermia to attempt to correct the "shock" which they believed had supervened with the fall in temperature. However, the reports of the reductions in cardiac work and oxygen demand led surgeons to test and adopt the technic of hypothermia as an adjunct in cardiovascular surgery.

As hypothermia develops, not only does the blood pressure fall, but severe vasoconstriction occurs in the skin and in the limbs. One organ after another becomes "closed off" from the circulating blood stream, and at the low body temperatures, seen most dramatically in extreme hypothermia, the circulation is restricted

* This effect has recently been confirmed (W. M. Manger, K. G. Wakim, and J. L. Bollman: Effect of increased intracranial pressure on pressor amine concentration in blood. Federation Proc. **14:** 98, 1955).

to the most vital organs: brain, heart and lungs.

Some vascular responses to hypothermia depend on the direct action of primitive thermosensitive centers in the hypothalamus,[14] acting through the final common pathway of the vasomotor center. Thus, even in animals without capacity for temperature regulation, direct warming of the hypothalamic region produces a rise in blood pressure, while cooling of this part of the brain brings about a fall in blood pressure. The "setting" of these diencephalic thermosensitive centers may thereby influence the final level of the blood pressure.[17]

It has long been known that the hypothalamus elaborates at least one vasopressor material which is then stored in the posterior pituitary;[18] however, no satisfactory evidence has yet been advanced to show that this principle plays a physiologic role in blood pressure regulation. Recent work on the anatomy and physiology of the hypothalamus has shown its nuclei to be capable of secreting other potent hormones which may affect salt and water balance as well as the ultimate control of some of the endocrine glands.[18] The role of the hypothalamus in blood pressure regulation and in hypertension may prove highly important.

The higher centers in the brain likewise play significant roles in blood pressure responses to pain and anxiety. Some of the potential functional connections can be demonstrated by direct stimulation of many sensory regions. All these central mechanisms operate via the autonomic nervous system to regulate vascular tone. Aside from the direct neurogenic connections to the vessels, the presence in the blood stream of circulating catechol-amines probably plays an important role in determining the total peripheral resistance.

The Epinephrines. The delay between the discovery of a potent biologic agent and the acceptance of its physiologic role is well exemplified by the epinephrines. For several decades these substances were generally believed to play no important role in blood pressure regulation, despite the insistence of that far-sighted physiologist, the late Walter B. Cannon. In recent years the studies of von Euler and his group in Sweden, and of Goldenberg[20] in this country, have clarified some of the mechanisms whereby these substances may participate in circulatory regulations.

Epinephrine, arising primarily from specialized cell groups in the adrenal medulla,[21] produces numerous adjustments of the circulation as well as important metabolic effects. It induces vasodilatation in the striated muscles and in the liver while producing vasoconstriction in the kidneys and skin. Its metabolic effects include significant rises in oxygen consumption, in body temperature, and in blood sugar.[6] Psychogenic effects may include a transient sense of anxiety with visceral distress (butterflies) and increased irritability.[6]

By contrast, norepinephrine, similar chemically, except that it has one less methyl group, is primarily a cardiovascular hormone. This substance, found in the adrenal medulla, spleen, liver and heart is produced primarily in the sympathetic nerves where it apparently acts as a neurohumoral transmitter. Norepinephrine produces generalized arteriolar constriction except in the coronary vessels (which it dilates) and an increased strength of contraction (positive inotropism) of the heart, without direct effects on the heart rate.

The potential roles of these two hormones in the regulation of blood pressure has been brought into clearer focus by studies of tumors of the adrenal medulla (pheochromocytomas), and of the sympathetic ganglia (paraganglionomas). These tumors, containing large quantities of the two epinephrines, are associated with the excretion of abnormal quantities of catecholamines in the urine.[20] Extracts of the tumors show variable quantities of the two substances.

When high concentrations of epinephrine are released continuously by such a tumor, metabolic effects may predominate with an increased metabolic rate, a heightened body temperature, blood sugar, enhanced sweating, irritability and anxiety.[22] When the tumor releases norepinephrine principally, the excess hormone may reveal itself primarily as a paroxysmal or even as a persistent hypertension.

The rate of secretion of these tumors can

be assayed by the urinary output which contains 1 to 2 per cent of the total amount being delivered into the blood stream. A small quantity of these catechol-amines appears ordinarily in the urine of normal man (30 μg. per day); this increases several-fold in the standing position and in exercise, and is reduced when the subject lies down. By producing vasoconstriction in the dependent parts of the body, the circulating epinephrines appear to play a physiological role in reflexes which act against orthostatic or postural hypotension.

The clinical importance of these responses has been demonstrated by Luft and von Euler[23] who have shown that some patients with postural hypotension excrete subnormal quantities of the catechol-amines. Administration of norepinephrine to such subjects eliminates the symptoms induced by standing. Postural hypotension may therefore be looked upon as a type of neurohormonal deficiency disease. By contrast, subjects under emotional tension excrete increased quantities of these substances.[24]

It is but a step in concept from decreased secretion in postural hypotension to hypersecretion in essential hypertension. This is a step for which suggestive data have become available, but one which will require extensive documentation. About 15 per cent of patients with essential hypertension do excrete an abnormally high quantity of catechol-amines in the urine.[25] The influence of the central nervous system on the blood pressure level is of potential importance in such cases. This is indicated by secretion of the epinephrines in predictable quantities after stimulation of specific areas of the hypothalamus in animals.[26]

Hökfelt[21] has recently demonstrated two discrete types of islands in the adrenal medulla, one of which apparently secretes epinephrine while the other secretes norepinephrine. These results, along with those already cited on quantitative norepinephrine release induced by intracranial compression, signal the emergence of a concept of the *specificity* of sympathadrenal function to replace the common notion that the sympathetic nervous system can respond only by diffuse generalized discharge. Thus, depending on the reflex pathway stimulated, activation of one particular group of responses provides for the correction of a vascular disturbance; under other circumstances primarily metabolic responses may be activated. This would provide the sympathetic nervous system with that delicate degree of vasomotor control which heretofore has been segregated to the parasympathetic nervous system.

Carotid Mechanisms

In recent years the attention given to the general problem of hypertension has gradually moved from preoccupation with the kidney and returned to the nervous system. The extensive literature on the carotid-sinus mechanisms has done much to bring about a new understanding of the important role of the pressor-receptor mechanisms which participate in the regulation of the blood pressure.[9] Like the receptors in the root of the aorta, the carotid sinus acts as an outpost of the brain, testing the blood for its pressure level, so that the vasomotor center may be properly advised. In similar fashion, the adjacent carotid body samples the blood for its oxygen and carbon dioxide content, for pH, and probably for other qualities.

Disturbances in blood pressure regulation may stem from the fact that the walls of the sinuses can respond directly to the effect of vasoactive drugs. For example, when epinephrine is applied directly to the carotid sinuses, there is an increase in the number of impulses passing from these receptors to the vasomotor centers, and this is followed almost at once by a fall in the peripheral resistance and in the blood pressure.[9] Contrariwise, the direct application of vasodilator materials, such as acetylcholine or papaverine to the sensitive sinus walls reduces the number of impulses originating in them, and a rise in blood pressure follows. Just exactly how these mechanisms play a role in the delicate balance of the normal blood pressure is not adequately understood. However, that they can play some such role may be inferred from the work of Wakerlin,[27] who has shown in the dog that encasement of

both carotid sinuses in plastic casts results in the development of a progressive arterial hypertension.

Hypotensive Blocking Agents

Attempts to interrupt the mechanisms responsible for hypertension have focused on the capacity of the sympath-adrenal system to elevate the blood pressure above the normal level. Pharmacological agents and surgical techniques have been applied to all levels of this control system to block its connections with the blood vessels. Thus, rauwolfia, an herbal long used as a sedative in India has now come into considerable vogue as an antihypertensive agent.[28] This drug acts on the blood pressure primarily by its depressant action on the higher nervous centers, reducing emotional tone and anxiety. The veratrum alkaloids, employed with some success in the management of hypertensive crises, also operate through the higher centers, apparently by reflexly inhibiting vasoconstriction.

Long experience with partial or complete surgical ablation of the sympathetic ganglia has indicated that in many instances a fall in blood pressure from abnormally high levels ensues.[29] Pharmacologic blocking agents such as pentapyrrolidinium, hexamethonium and tetraethylammonium, reduce the ability of the sympathetic nervous system to control the blood vessles and these have been utilized as symptomatic anti-hypertensive agents. Hydrazinophthalazine apparently has a twofold action, depressing the higher centers responsible for vasomotor regulations, as well as acting as a blocking agent at the autonomic and perhaps even at the vascular level. Among the latter, its role in increasing renal blood flow has been stressed. Finally, benzodioxane and dibenamine produce their ephemeral blood pressure lowering effects by blocking the pressor effects of circulating catechol-amines.

Salutary responses to these drugs become most evident when the patient is in the upright position, permitting pooling of some of the circulating blood volume in the dependent limbs and viscera. The reflex vasomotor tone normally evoked to prevent the gravitational displacement of this volume from the circulation stream is eliminated and a depressor effect results.[30]

Thoracic Receptors

One of the recent trends in the field of neurogenic control has been the general appreciation of the fact that pressor receptors are ubiquitous. This is true not only for the systemic vessels but for the intrathoracic structures as well. Important specialized receptors have also been demonstrated in the great veins and in the heart itself.[31-35] For example, each of the venous pressure waves (a, c and v) may be accompanied by a volley of impulses along the nerves from the atria to the vasomotor center. Other receptors in the ventricular septum give brief discharges during the isometric contraction phase.[36] Equally sensitive receptors lie in the pulmonary vasculature and in the lung walls themselves; still others can be shown to be present in the coronary blood vessels. These multitudinous receptors, sending impulses to the brain, operate together to vary the level of the action of the vasomotor center and thereby may affect the blood pressure level.

Pulmonary Vasculature

The regulation of the pulmonary and systemic vasculature are closely interlinked. This is dependent (1) upon the relative power of the two ventricles whose function must be in balance; (2) upon the redistribution of blood by changes in the capacity of the systemic circuit and its reservoirs; and (3), as is becoming more and more evident, upon an interchange of neurohumoral signals.

The reflex regulation of the pulmonary blood flow is undoubtedly intimately associated with the ventilatory function of the lung. The relative roles of direct control of the pulmonary blood vessels and indirect control through the extravascular mechanisms are still being evaluated. Some of our newer views on the regulation of the pulmonary circulation have already been presented.[37]

Only recently we have been able to demonstrate that miliary pulmonary emboli confined to one lung can lead to pulmonary arterial

hypertension and to bilateral pulmonary edema.[38] The contralateral edema was not dependent upon a purely hydrostatic effect nor local vascular injury but seemed to depend on neurohumoral mechanisms. The pulmonary hypertension was due to a neurohumoral mechanism acting upon the peripheral pulmonary vasculature, since the pulmonary arterial wedge pressure (and seemingly the pulmonary peripheral venous pressure) increased, while the left atrial pressure remained relatively normal. Furthermore, the sympathetic blocking agents, dibenamine and benzodioxane, definitely lessened contralateral pulmonary edema.

The neurohumoral interrelation between the pulmonary and systemic vasculature is easily demonstrated. A number of reflexes may be elicited by the injection of specific substances into the pulmonary or coronary circulations, bringing about a slowing of the heart, a fall in blood pressure as well as complex changes in respiration.[39] These have their afferent pathways in the vagus and reflexly influence both vagal and sympathetic tone. For example, the injection of veratridine directly into a coronary artery causes a profound reflex fall in systemic blood pressure (Bezold reflex). Injection of a variety of other pharmacological substances into the pulmonary artery causes a systemic peripheral dilatation associated with a fall in blood pressure, heart rate and cardiac output.[39] It is of interest that a naturally occurring substance, serotonin, also can elicit these Bezold-type reflexes. Their exact physiological and clinical role is still conjectural, although they may well play a role in the distressing hypotensions which sometimes follow acute coronary occlusion or pulmonary embolism. Vasovagal collapse leading to fainting may also originate in such cardiopulmonary reflexes, although the systemic vasodilation is probably the mechanism of the acute shock-like picture.[6]

Recent studies on some patients with metastatic carcinoid have suggested that circulating serotonin, perhaps released during nervous stimulation, may have a vasoregulating role. Physiologically, it is known that the injection of serotonin (5-hydroxytryptamine, a derivative of tryptophane) may cause a marked rise in the pulmonary arterial pressure through some action on the pulmonary vessels as well as through bronchoconstrictor mechanisms.[40]

In patients with these slow growing argentaffinomas, a particular type of vascular flushing may occur in the butterfly area of the face when the patient is emotionally disturbed.[41-42] While systemic blood pressure changes have not been detected, indirect evidence suggests an effect on the lesser circulation. A loud systolic murmur over the left precordial base may develop, and at autopsy a type of pulmonic valvular stenosis (possibly acquired) may be found. These clinical findings may be interpreted as suggesting that an enterogenic vasoactive material released on central nervous stimulation may act on the pulmonary vascular resistance to determine a malignant cardiovascular chain of events.

Thus, the products of the chromaffin cells of the body, originating from the neural crest and producing epinephrine, nor-epinephrine, serotonin and probably other substances, may represent important aspects of the neurogenic control of the circulation. These neurohumors join with direct neurogenic impulses to control the calibre of the blood vessels of both the lesser and greater circuits.

Conclusion

The physiological need to control the degree of constriction of the various vascular beds in the body has apparently led to the development of a large variety of regulatory mechanisms. These have assumed a complex and purposeful homeostatic role, capable of adjusting the distribution of blood according to need and in relation to an established hierarchy of organ priorities. These vasoactive mechanisms operate not only locally but also at a distance through neurogenic and neurohumoral pathways. They involve all aspects of the central nervous system and its visceral sensory and motor mechanisms. In competition with the local requirements for blood, they maintain

the blood pressure at a level acceptable to the barostatic apparatus by denying a luxus supply to the less vital organs if this is necessary, though ready to divert blood to them temporarily when this is imperative.

Experimental and clinical studies in health and disease on man and animals will unravel the relative importance of these complex neurohumoral mechanisms. These undoubtedly will form a more adequate basis for the understanding of the role of the nervous system in shock and hypertension and ultimately pave the way for a more rational approach to the therapeusis of these and other common vascular disorders.

REFERENCES

[1] Katz, L. N. and Leiter, L.: The present conception of "essential" hypertension. A. Physiological and clinical correlation. Psychosom. Med. **1:** 101, 1939.

[2] — and Rodbard, S.: The integration of the vasomotor responses in the liver with those in other systemic vessels. J. Pharmacol. & Exper. Therap., **67:** 407, 1939.

[3] —: Factors controlling the coronary circulation. Arch. Inst. cardiol. México **14:** 30, 1944.

[4] Rodbard, S.: Blood pressure regulatory mechanisms and salt water exchanges. Proc. Council for High Blood Pressure Research, Am. Heart A. **2:** 42, 1953.

[5] Stamler, J., Katz, L. N., Pick, R. and Rodbard, S.: Dietary and Hormonal Factors in Experimental Atherogenesis and Blood Pressure Regulation. *In*, Recent Progress in Hormone Research, Gregory Pineus, ed. New York, Academic Press, 1955, in press.

[6] Barcroft, H. and Swan, H. J. C.: Sympathetic control of human blood vessels. London, E. Arnold & Co., 1954.

[7] Cushing, H.: Some experimental and clinical observations concerning states of increased intracranial tension. Am. J. M. Sc. **124:** 375, 1902.

[8] Rodbard, S. and Saiki, H.: Mechanism of the pressor response to increased intracranial pressure. Am. J. Physiol. **168:** 234, 1952.

[9] Heymans, C.: Sino-aortic receptors. Proc. International Physiological Congress **19:** 44, 1953.

[10] Rodbard, S., Reyes, M., Mininni, G. and Saiki, H.: Neurohumoral transmission of the pressor response to intracranial compression. Am. J. Physiol. **176:** 341, 1954.

[11] — and Stone, W.: Pressor mechanisms induced by intracranial compression. Circulation, in press.

[12] —: Relationship between body temperature and arterial pressure. Proc. Soc. Exper. Biol. & Med. **63:** 43, 1946.

[13] — and Tolpin, M.: A relationship between the body temperature and the blood pressure in the chicken. Am. J. Physiol. **151:** 509, 1947.

[14] —: Body temperature, blood pressure and hypothalamus. Science **108:** 413, 1948.

[15] —, Saiki, H., Malin, A. and Young, C.: Significance of changes in plasma and extracellular volumes in induced hyperthermia and hypothermia. Am. J. Physiol. **167:** 485, 1951.

[16] Prec, O., Rosenman, R., Braun, K., Rodbard, S. and Katz, L. N.: The cardiovascular effects of acutely induced hypothermia. J. Clin. Invest., **28:** 293, 1949.

[17] Rodbard, S., Samson, F. and Ferguson, D.: Thermosensitivity of the turtle brain as manifested by blood pressure changes. Am. J. Physiol., **160:** 402, 1950.

[18] Scharrer, E. and Scharrer, B.: Hormones produced by neurosecretory cells. Recent Progress in Hormone Research, New York, Academic Press, 1954.

[19] McQueen, J. D., Browne, K. M. and Walker, A. W.: Role of the brainstem in blood pressure regulation in the dog. Neurology **4:** 1, 1954.

[20] Goldenberg, M., Serlin, I., Edwards, T. and Rapport, M. M.: Chemical screening methods for the diagnosis of pheochromocytoma. Am. J. Med., **16:** 310, 1954.

[21] Hökfelt, B.: Personal communication.

[22] Smithwick, R. H., Greer, W. E. R., Robertson, C. W. and Wilkins, R. W.: Pheochromocytoma. New England J. Med. **242:** 252, 1950.

[23] Luft, R. and von Euler, U. S.: Two cases of postural hypotension showing a deficiency in the release of norepinephrine and epinephrine. J. Clin. Invest. **32:** 1065, 1953.

[24] von Euler, U. S. and Lundberg, U.: Effect of flying on the epinephrine excretion in air force personnel. J. Appl. Physiol. **6:** 551, 1954.

[25] —: Catechol amine Excretion in Urine in Cases of Hypertension. *In*, Ciba Foundation Symposium on Hypertension: Humoral and neurogenic factors. Wolstehome, G. E. W. and Cameron, M. P., eds. Boston, Little, Brown and Co., 1954.

[26] Folkow, B. and von Euler, U. S.: Selective activation of noradrenaline and adrenaline producing cells in the cat's adrenal gland by hypothalamic stimulation. Circulation Research **2:** 191, 1954.

[27] Wakerlin, G. E., Crandall, E., Frank, M. H., Johnson, D., Pomper, L. and Schmid, H. E.: Experimental hypertension produced by constriction of the carotid sinus area. Circulation Research **2:** 416, 1954.

[28] Wilkins, R. W.: Clinical usage of Rauwolfia alkaloids, including reserpine. Ann. New York Acad. Sc. **59:** 36, 1954.

[29] SMITHWICK, R. H.: Surgical treatment of hypertension. Am. J. Med., **4:** 744, 1948.

[30] ALLEN, E. V. AND MACLEAN, A. R.: Relief of hypertension headache with head-up bed. Proc. Staff Meet., Mayo Clin. **15:** 523, 1946.

[31] KATZ, L. N. AND SAPHIR, O.: The nerve plexus between the aorta and pulmonary artery. I. Observations on its nature and function. Am. J. Physiol. **104:** 253, 1933.

[32] MAYNE, W. AND KATZ, L. N.: Observations on the path taken by the pain fibers from the heart. Am. J. Physiol. **114:** 688, 1936.

[33] KATZ, L. N. AND JOCHIM, K.: Observations on the innervation of the coronary vessels of the dog. Am. J. Physiol. **126:** 395, 1939.

[34] MALINOW, M. R., KATZ, L. N. AND KONDO, B.: Is there a vagal pulmonocoronary reflex in pulmonary embolism? Am. Heart J. **31:** 702, 1946.

[35] BALLIN, I. R. AND KATZ, L. N.: Observations on the localization of the receptor area of the Bainbridge reflex. Am. J. Physiol. **135:** 202, 1941.

[36] WHITTRIDGE, D.: Electrophysiology of afferem cardiac and pulmonary fibers. Proc. International Physiological Congress **19:** 66, 1953.

[37] RODBARD, S.: Bronchomotor tone: a neglected factor in the regulation of the pulmonary circulation. Am. J. Med. **15:** 356, 1953.

[38] KATZ, L. N., PICK, R., LARRAIN, J. R., LEVINSON, I., LAURENT, D. N. AND GOLD, H.: Consequences of miliary pulmonary embolization in dogs. In preparation.

[39] DAWES, G. S.: Reflexes from the heart and lungs. Proc. International Physiological Congress **19:** 51, 1953.

[40] — AND COMROE, J. H., JR.: Chemoreflexes from the heart and lungs. Physiol. Rev. **34:** 167, 1954.

[41] BIÖRCK, G., AXÉN, O. AND THORSON, Å.: Unusual cyanosis in a boy with congenital pulmonary stenosis and tricuspid insufficiency. Fatal outcome after angiocardiography. Am. Heart J. **44:** 143, 1952.

[42] THORSON, Å., BIÖRCK, G., BJORKMAN, G. AND WALDENSTROM, J.: Malignant carcinoid of the small intestine with metastases to the liver, valvular disease of the right side of the heart (pulmonary stenosis and tricuspid regurgitation without septal defects), peripheral vasomotor symptoms, bronchoconstriction and an unusual type of cyanosis. Am. Heart J. **47**; 795, 1954.

ABSTRACTS

PATHOLOGIC PHYSIOLOGY

Theelan, E. O., Paul, M. H. and Gregg, D. E.: A Comparison of Effects of Intra-Arterial and Intravenous Transfusion in Hemorrhagic Hypotension on Coronary Blood Flow, Systemic Blood Pressure and Ventricular End Diastolic Pressure. J. Appl. Physiol. **7:** 248 (Nov.), 1954.

The preferential use of intra-arterial or intravenous blood transfusions in the treatment of shock is an important clinical problem. The intra-arterial route has been favored because of the assumptions that: (1) this route produces a more rapid increase in systemic pressure as a result of a hydropic effect; (2) the perfusion of the coronary bed is more quickly and effectively re-established; and (3) that a larger volume of blood can be given without producing dangerous elevations of venous pressure and right ventricular dilatation. The experiments were designed to study the effects of comparable blood transfusions by the arterial and venous routes in the same dog, made hypotensive due to hemorrhage on systemic blood pressure, right ventricular end diastolic pressure, left ventricular end diastolic pressure, and coronary blood flow.

Twelve experiments were accomplished in mongrel dogs. Pressure determinations were made from the carotid artery, right ventricle, and left ventricle with Gregg optical manometers or strain gauges. Coronary blood flow was measured by a rotameter. Readings were taken before, during a hypotensive period (arterial pressure between 5 and 57 mm. Hg), and during reinfusion of blood intra-arterially or intravenously.

There were no significant differences between intra-arterial or intravenous infusion with respect to time required for pressure restoration or the final pressure level reached in the carotid artery, right ventricle and left ventricle. The two routes of infusion were equally effective in restoring coronary blood flow.

WECHSLER

Johnson, D. H.: The Effect of Hemorrhage and Hypotension on the Liver Blood Flow. J. Physiol. **126:** 413, 1954.

It has been shown that prolonged hypotension causes a depression of liver blood flow and metabolism, and it has been postulated that one result of this may be an accumulation of toxic materials, e.g., V.D.M., which may contribute to circulatory collapse. Changes in liver blood flow during hypotension were, therefore, measured in anesthetized rats by means of internal colorimetry (Grayson, 1952). Hypotension was induced by hemorrhage into a reservoir and then the blood was reinfused.

In 25 experiments, there was an initial rapid decrease and partial recovery in liver blood flow followed by progressive diminution. Interruption of the arterial blood supply to the liver (ligation of the coeliac axis) before bleeding failed to alter this response. Ligation of the hepatic nerves, along with the coeliac axis, prevented the initial rapid fall and partial recovery in liver blood flow. Interruption of nerve supply by tetraethyl ammonium bromide or dibenamine caused a more gradual drop in flow in response to hemorrhage. Intermittent graded reductions in arterial pressure (10 mm. Hg each) produced a transitory fall in flow lasting only a few minutes. After a critical level of blood pressure (approximately 60 mm. Hg) was reached, full recovery of flow did not occur. Separate interruptions of the arterial or portal blood supplies did not alter these results. Reinfusion of the blood brought about an increase in liver blood flow at rates substantially below those recorded at the beginning of the experiments.

These results suggest that the initial rapid fall and

partial recovery (transient reflex hepatic vasoconstriction) in flow were nervously mediated in response to the low blood pressure. Because liver blood flow is maintained at near normal values despite the decrease in perfusion pressure to a critical level, an internal blood flow regulating mechanism in the liver is postulated. Hypotension causes progressive increase in hepatic resistance to portal blood flow which is independent of nervous influences and persists after termination of hypotension.

WECHSLER

Branwood, A. W.: Primary Pulmonary Hypertension. Edinburgh M. J. **61:** 332 (Oct.), 1954.

Three cases of primary pulmonary hypertension are described. The main findings in these cases were (a) right ventricular hypertrophy, (b) dilatation of the main pulmonary vessels, (c) atheroma of these vessels, and (d) arteriolosclerosis of the pulmonary arterioles.

The above changes are identical with those seen in the systemic circulation in essential hypertension. In both diseases the etiology is, as yet, unknown. In primary pulmonary hypertension, there would appear to be an increased tonus of the pulmonary arterioles. The right ventricular hypertrophy and the dilatation of the main pulmonary artery seen in the cases described would appear to be due to the elevated pulmonary pressure. Another feature in common between systemic hypertension and primary pulmonary hypertension are the identical changes in the respective vascular beds. These changes, in both instances, may range from normal vessels to obliterative arteriolosclerosis. The hall mark of prolonged systemic hypertension is found in the arterioles, the changes in the pulmonary arterioles would therefore indicate pulmonary hypertension as the cause of the vascular sclerosis in these cases.

BERNSTEIN

Brody, T. M., Palmer, J. F., and Bennett, D. R.: Phosphorylation in Cardiac Muscle from Failing and Unfailing Heart-Lung Preparations. Proc. Soc. Exper. Biol. & Med. **86:** 739 (Aug.–Sept.), 1954.

Oxygen uptake as well as inorganic phosphate uptake by cardiac muscle were measured manometrically and the oxygen-phosphate ratio calculated. This was done on normal canine cardiac muscle and failed canine cardiac muscle. There was no difference in the phosphorylating ability noted between these two muscle preparations. The authors conclude that this indicates (if energy metabolism is concerned in failure) the defect is not in the production of energy-rich compounds.

HARVEY

Ross, E. J. and Spencer, A. G.: Observations on Cation Exchange Resins in the Small and Large Intestines. Clin. Sc. **13:** 555 (Nov.), 1954.

The authors describe their method for determining Na and K transfers on and off a sulfonated polystyrene resin in isolated loops of small and large intestines of the rat. By employing the radioactive isotopes of Na and K, it was possible to calculate the absolute rates of transfer as well as the net exchange. In the small intestine, the net rate of Na uptake was 1.0 mEq. per Gm. per hour. In the large intestine, the transfer of Na off the resin exceeded the uptake, leaving a net transfer of -0.35 mEq. per Gm. per hour, while the net rate of K uptake was $+0.38$ mEq. per Gm. per hour.

These observations imply that exchange resin in the intestine acts as an additional electrolyte-containing compartment capable of coming into equilibrium with the exchangeable Na and K of the body. Transfers of these cations between the body and the resin occur in a constantly changing series of dynamic equilibria as the resin passes down the intestinal tract. Indeed, at equilibrium, the transfers on the resin equal the transfers off, so that there is no further net exchange in that segment of gut. The relative proportions of cations in the surrounding fluid is the main factor in determining the equilibrium concentrations of cations on the resin. The remarkably efficient Na-conserving ability of the colon is stressed. The mechanisms involved appear to be first reabsorption of the bulk of the water and electrolytes, and also a quantitative cationic exchange of K for Na.

ENSELBERG

Marshall, R., Stone, R. W. and Christie, R. V.: Relationship of Dyspnea to Respiratory Effort in Normal Subjects, Mitral Stenosis and Emphysema. Clin. Sc. **13:** 625 (Nov.), 1954.

Intra-esophageal pressure and tidal volume were recorded in normal subjects, patients with mitral stenosis, and patients with emphysema at varying grades of exercise up to the maximum they could maintain for six minutes. The results on normal subjects breathing without or against an inspiratory resistance, suggest that the factor limiting respiratory effect is the force exerted on the lungs. This dyspnea threshold is not affected by inspiratory resistance.

The patients with mitral stenosis or emphysema reached their limit of respiratory effort while exerting as great a force on the lungs as the normals but at a much lower rate of ventilation. For example, a patient with mitral stenosis who reaches his limit of respiratory effort when breathing 30 or 40 L per minute, may be exerting the same force on his lungs as a normal person whose limit is reached when breathing 120 L. per minute. The results suggest that in order to satisfy a respiratory stimulus a person can increase the minute volume until he is limited by the force which he can apply to the lungs. The maximum rate of physical work he can perform will depend not only on the minute volume

required at this rate but also on the resistance of the lungs to expansion.

ENSELBERG

Merger, John H.; Miller, S. I. and Snyder, H.: Effect of Increased Jugular Pressure on Cerebral Hemodynamics. J. Appl. Physiol. **7:** 245 (Nov.), 1954.

It has been suggested that cerebral blood flow might be impaired in heart failure as a result of increased venous pressure which is associated with this disease. The purpose of this study was to determine the effect of increased jugular venous pressure in cerebral blood flow and, therefore, to investigate the above hypothesis.

In seven patients, measurements of cerebral blood flow (by the N_2O technic of Kety and Schmidt), jugular venous pressure, cerebrospinal fluid pressure, mean arterial blood pressure, blood gases and hematocrit were made before and five minutes after the jugular bulb venous pressure was raised to 124–300 mm. of water. The jugular bulb venous pressure was elevated by raising the pressure in a blood pressure cuff securely fastened around the neck as a tourniquet.

The increased jugular venous pressure failed to change cerebral blood flow, cerebrovascular resistance, mean arterial blood pressure, pulse rate, hematocrit or respiratory rate. However, there was a significant increase in cerebral O_2 consumption, arterial O_2 content and cerebrospinal fluid pressure.

These results indicate that a moderate increase in venous pressure (not in excess of 300 mm. H_2O) does not affect the cerebral circulation.

WECHSLER

Guyton, A. C., Polizo, D. and Armstrong, G. G.: Mean Circulatory Filling Pressure Measured Immediately After Cessation of Heart Pumping. Am. J. Physiol. **179:** 261 (Nov.), 1954.

In this study action of the heart was stopped suddenly by ventricular fibrillation, vagus standstill or acute pulmonary artery occlusion. Immediately afterwards blood was perfused from aorta to external jugular vein. In normal dogs under these conditions the mean circulatory filling pressure was 6.3 mm. Hg (average). Total spinal anesthesia reduced it to 5 mm Hg. Continuous maximal injections of epinephrine to increase vasomotor tone increased it to 16 mm. Hg. Slow pulmonary artery occlusion gave a maximum mean circulatory filling pressure of 13 mm. Hg. This represented the sympathetic activity produced by the animal. Infusion of fluid before standstill was produced elevated the mean circulatory filling pressure.

OPPENHEIMER

Dudley, H. F., Boling, E. A., Le Quesne, L. P. and Moore, F. D.: Studies on Antidiuresis in Surgery: Effects of Anesthesia, Surgery and Posterior Pituitary Antidiuretic Hormone on Water Metabolism in Man. Ann. Surg. **140:** 354 (Sept.), 1954.

A study on the renal excretory capacity for water in the immediate postoperative phase was performed on a group of patients undergoing major abdominal surgery and compared with the responses in a series of normal subjects. In each instance an intravenous infusion of 5 per cent glucose was given. The type of change suggested that following major surgery and anesthesia, posterior pituitary antidiuresis occurred, producing a diminished renal excretory capacity, a finding to be borne in mind in prescribing postoperative fluids.

ABRAMSON

PATHOLOGY

O'Brien, W.: Endocardial Fibrosis in the Sudan. Brit. M. J. **2:** 899, (Oct. 16) 1954.

In the laboring class endocardial fibrosis is the most frequent cause of congestive heart failure. It appears to occur as often in Arabs as in Negroes. Embolism from mural thrombi is often the "opening gun." Syphilis is clearly not a factor. Undernutrition or malnutrition cannot be incriminated. Eosinophilia was present in only two cases.

MCKUSICK

Fisch, C. and Evans, P. V.: The Heart in Dystrophia Myotonica. Report of an Autopsied Case. New England J. Med. **251:** 527–529 (Sept. 23), 1954.

The case of a man, aged 41 years, with *dystrophia myotonica* is described. Symptoms began about 10 years before he died quite suddenly. Clinical and electrocardiographic observations 10 days before his death disclosed atrial flutter with varying degrees of atrioventricular block. Microscopic examination of the myocardium of the left ventricle disclosed diffuse fibrosis with separation of muscle fibres by fairly dense, fibrous connective tissue. Hypertrophied muscle fibres with large rectangular nuclei were scattered throughout the left ventricular myocardium. The coronary vessels were normal. It is felt that the cardiac involvement caused the patient's death.

ROSENBAUM

Saphir, O. and Field, M.: Complications of Myocarditis in Children. J. Pediat. **45:** 457 (Oct.), 1954.

This study was undertaken to ascertain what, if any, complications may arise in instances of myocarditis. Of 40 cases of myocarditis observed during the last eight years, 15 fulfilled the criteria of isolated myocarditis. Outstanding were the findings of minute emboli in the coronary arteries and cerebral vessels. The sources of these emboli were small mural thrombi in the heart, although these were found only in three cases. These thrombi were discovered by chance in the available section of the

myocardium and adjacent endocardium. The fact that often multiple emboli were present in several organs, speaks for the heart as the source of the emboli. The cause of these emboli is obviously the inflammatory changes close to the endocardium producing subendocardial edema or even localized foci of mural endocarditis predisposing to the formation of thrombi. It seems quite clear that multiple emboli constitute a serious complication contributing to the death of the patients.

BERNSTEIN

Wacker, W. and Merrill, J. P.: Uremic Pericarditis in Acute and Chronic Renal Failure. J.A.M.A. **156:** 764 (Oct. 23), 1954.

This paper reports the occurrence of pericarditis in patients with acute renal failure and compares this with the occurrence in chronic renal failure. The hospital records of 77 patients with acute renal failure of varying causes were reviewed. Pericardial friction rub was heard in 14 of 77 patients, or 18 per cent. Of this group six survived and eight died. Postmortem examinations done in six of the patients who died showed morphological evidence of pericarditis. Forty-three patients dying of chronic renal failure were studied. Twenty-two of these had pericarditis diagnosed clinically and at necropsy. Of the group of patients with acute pericarditis associated with acute renal failure pain was either absent or not mentioned in 13 of the 14 cases. Of the 22 patients with chronic renal failure and pericarditis, eight complained of pain. This study shows that pericarditis occurs in about 18 per cent of cases of acute renal failure but does not have the same grave prognostic significance as it has in chronic renal failure; and that pericarditis occurs in about half of the patients dying of chronic renal failure. In keeping with the findings of other studies these clinical observations suggest that precordial pain of a pleuritic type occurs in many patients with uremic pericarditis and pain referred to the left shoulder occurs in about half of the patients who have painful pericarditis.

KITCHELL

PHARMACOLOGY

Garb, S. and Venturi, V.: The Differential Actions of Potassium on the Therapeutic and Toxic Effects of Ouabain. J. Pharmacol. & Exper. Therap. **12:** 94 (Sept.), 1954.

Potassium antagonized the arrhythmia producing effects of the digitalis glycosides. However, it is questionable if K^+ antagonizes other actions of the digitalis glycosides. This problem has both academic and clinical importance.

The contractile force and threshold of irritability of cat papillary muscle which was stimulated electrically was measured after adding K^+ and ouabain at various concentrations. K^+ either increased or did not interfere with the contractile force produced by ouabain. K^+ did not change the threshold of irritability until the concentration of ouabain caused a decreasing inotropic effect.

These results indicate that K^+ concentrations of 3.5 to 8.5 millimols per liter did not interfere with the inotropic action of ouabain and they protected the mammalian ventricular muscle against ouabain produced arrhythmias.

WECHSLER

Abreu, B. E., Richards, A. B., Alexander, W. M., and Weaver, L. C.: Cardiovascular, Emetic and Pharmacodynamic Properties of Certain Veratrum Alkaloids. J. Pharmacol. & Exper. Therap. **12:** 73 (Sept.), 1954.

It has been demonstrated that protoveratrine is not a single substance but is made up of chemically different substituents. It is important to know to what extent these substituents affect hypotensive potency. Arterial blood pressure was measured in anaesthetized dogs. Hypotensive potencies were determined by the carotid sinus pressor reflex procedure of Rubin and Burke (1953). The influence of slight structural differences of acid groups on hypotensive potencies was indicated by the facts that Protoveratrine A, Veralba and Germitetrine B have the same and greatest potencies, Protoveratrine B the next greatest, and Unitensen the least. Various substituents were given intravenously in order to compare the emetic and hypotensive activities. Protoveratrine A and Veralba were more potent emetics than Unitensen. There were no differences in the hypotensive emetic ratios and therefore no dissociation of hypotensive from emetic activity.

Studies on reflexes in dogs indicated that Protoveratrine A decreased blood pressure by acting on receptors whose impulses travel to the vasomotor center via the vagus and carotid sinus nerves.

WECHSLER

Echenhoff, J. E. and Dripps, R. D.: The Use of Norepinephrine in Various States of Shock. Anesthesiology **15:** 681 (Nov.), 1954.

The authors analyze and discuss their experience with norepinephrine in patients with severe cardiovascular collapse of various etiology. Some of the possible causes of the failures observed are discussed. In certain individuals, adequate pressor response can only be obtained with large doses such as 20 to 40 micrograms per minute and, therefore, inadequate dosage of norepinephrine may account for some failures. In other instances, the drug may fail to reach the site of action because blood is pooled in dilated vessels or the blood vessel may be unable to respond to the drug because of poor nutrition resulting from shock. Norepinephrine may also be ineffective because it is not properly distributed to the arterial circulation due to mechanical interference the venous blood return to the heart, inadequate blood volume, or cardiac failure. Al-

though norepinephrine is a valuable addition to the management of the patient in shock, the correction of the initiating factors still constitute the fundamental objectives in the treatment of shock.

SAGALL

Green, H. D., Shearin, W. T., Jr., Jackson, T. W., Keach, L. M. and Denison, A. B., Jr.: Isopropyl Norepinephrine Blockade of Epinephrine Reversal. Amer. J. Physiol. **179:** 287 (Nov.), 1954.

When adrenergic blockade was severe enough to give a pure skeletal muscle vascular bed vasodilator response with l-epinephrine, these experiments present evidence that constrictor endings are still being stimulated with an effectiveness by l-epinephrine equal to comparable doses of l-norepinephrine. The authors conclude that this persistent vasoconstrictor effect is masked by the simultaneous intense vasodilator response due to l-epinephrine.

OPPENHEIMER

Heiskell, C. L. Jr., Belsky, J. B. and Klaumann, B. F.: Treatment of Chronic Emphysema of Lungs With Diamox (Carbonic Anhydrase Inhibitor). J.A.M.A. **156:** 1059 (Nov. 13), 1954.

Chronic emphysema of the lungs, particularly if associated with cardiac complications, has long posed a therapeutic problem. Treatment, until recently, has been limited to the supportive measures and the conventional management of cor pulmonale. The primary problems of defective alveolar ventilation, increased carbon dioxide content of the blood, and respiratory acidosis have remained unsolved. Diamox proved useful in the treatment of four patients with chronic emphysema of the lungs. The venous plasma carbon dioxide combining power was decreased about 6 mEq. per liter during therapy. This coincided with a remarkably increased exercise tolerance, decreased dyspnea, and statistically significant improvement in performance of pulmonary function tests.

KITCHELL

Rea, E. L., Shea, J. and Fazekas, J. F.: Hypotensive Action of Chlorpromazine. J.A.M.A. **156:** 1249 (Nov. 27), 1954.

Seven patients were observed in whom acute hypotension developed after chlorpromazine administration. Hypotension detected early was easily reversed, but intensive therapy was required if the hypotension was of long duration. In one patient acute renal insufficiency subsequently developed, presumably a complication of the prolonged hypotension. Since some persons may be potential hypotensive reactors, blood pressure response should be determined at frequent intervals when the drug is first administered and whenever the dose is increased.

KITCHELL

Maren, T. H., Mayer, E. and Wadsworth, B. C.: Carbonic Anhydrase Inhibition. I. The Pharmacology of Diamox, 2-Acetylamino-1,3,4-Thiadiazole-5-Sulfonamide. Bull. Johns Hopkins Hosp. **95:** 199 (Nov.), 1954.

A detailed historical survey of carbonic anhydrase and its inhibitors from the discovery of the former in 1932 is provided. In man over 70 per cent of an administered dose of Diamox is excreted unchanged in the urine by 24 hours. When given in the therapeutic range of oral dosage Diamox can be detected in the plasma for 6 to 12 hours after administration but is detectable in the red cells for several days. Renal clearance is about ⅔ of simultaneously determined creatinine clearance in dog. The drug is distributed in a volume corresponding to "somewhat less" than 40 per cent of body weight in man, with about one-twentieth as high a concentration in C.S.F. and aqueous humor as plasma.

In the dog at least a 1000:1 ratio exists between toxic and therapeutic dosage of Diamox. In the mouse the LD 50 for the sodium salt is approximately the same as for sodium lactate or chloride.

Drowsiness and deep sleep, which may be induced in man with higher dosages, could not be produced in dogs, rats or monkeys at 25 times that dosage. The CNS effects in man are apparently due to reversible inhibition of brain carbonic anhydrase. No explanation for the striking species difference was apparent. The CNS effects of sulfanilamide are probably analogous.

For treatment of edema interrupted dosage seems desirable whereas in the treatment of epilepsy and glaucoma continuous maintenance therapy *may* be necessary.

In the animals no changes were observed in the crystalline lens which contains more carbonic anhydrase than any other tissue except the erythrocyte. However, no detailed morphological study of the lens was undertaken.

MCKUSICK

Counihan, T. B., Evans, B. M. and Milne, M. D.: Observations on the Pharmacology of the Carbonic Anhydrase Inhibitor "Diamox." Clin. Sc. **13:** 583 (Nov.), 1954.

Normal subjects were studied as well as patients with congestive failure due to rheumatic heart disease, hypertensive heart disease and pulmonary heart disease secondary to bronchitis and emphysema. Diamox increased the urinary volume, urinary pH, and the excretion of bicarbonate, sodium and potassium. However, the efficacy of the drug as a diuretic is limited by its self-inhibitory action. On repeated administration a systemic acidosis is produced with reduction of plasma bicarbonate and compensatory increase of chloride. The maximum excretion rate of bicarbonate then becomes less than 25 per cent of the amount filtered at the glomeruli. Diamox increases the maximum rate of water

diuresis, probably by a depressant action on the proximal tubular reabsorption of bicarbonate. In mild cases of congestive failure the drug acts very much as it does in normal subjects. In severe cases of cardiac failue it has a grossly abnormal action, resulting in the retention of sodium and excretion of potassium in amounts equal to the excess bicarbonate. In the cases of emphysema the authors found the drug to be of no more value than in other varieties of heart disease.

The authors consider that Diamox is relatively ineffective as a diuretic because the diuretic effect depends on increase of bicarbonate excretion. At therapeutic dose levels the maximum excretion rate of bicarbonate was less than 25 per cent of the amount filtered. While a similar limitation with respect to chloride applies to mercurial diuretics, the fact that plasma chloride concentration is four times that of bicarbonate results in a much higher maximal excretion rate of chloride. The self-limiting action of Diamox involves a systemic acidosis and consequent reduction of plasma bicarbonate. This can be restored only by stopping the drug or giving excess fixed base as sodium bicarbonate. The similar reduction of plasma chloride in mercurial diuresis on the other hand is easily corrected by the use of ammonium chloride.

And finally in severe cases of cardiac failure, Diamox may fail to remove sodium despite increased excretion of bicarbonate which is excreted entirely as the postassium salt. This could be a factor in potentiating digitalis toxicity.

ENSELBERG

Mulder, A. G., Gatz, A. H. and Tigerman, B.: Phosphate and Glycogen Determinations in the Hearts of Vitamin E-Deficient Rabbits. Am. J. Physiol. **179:** 246 (Nov.), 1954.

Rabbit hearts were damaged by vitamin E deficiency. Examination of these tissues showed a reduction of creatine phosphate to 0.9 mg. per cent from control values of 6.1 per cent. Glycogen, inorganic phosphate and adenosine polyphosphate were unchanged. A rapid onset of dystrophy and weight loss was associated with the largest decreases in cardiac creatine phosphate.

OPPENHEIMER

Cornell Conference on Therapy: How to Evaluate a New Drug. Am. J. Med. **17:** 722 (Nov.), 1954.

Clinical evaluation of new drugs is one of the major issues in therapeutic progress. The effect of a drug varies greatly with the patient's mood. The effect may also be significantly altered with a change in the mood. Special attention was directed to the use of the placebo, the double-blind test, statistical analysis of the data and experimental design to eliminate bias. Emphasis was placed on the unconscious aspects of bias of the physician. The control of bias by the double-blind test is now recognized as imperative for the valid evaluation of drugs, not only with respect to the study of subjective symptoms such as cardiac pain, but also in studies involving so-called objective measurements such as iron in anemia, diuretic agents and anticoagulants in thrombotic diseases. The conventional design of the treated and untreated groups in a clinical evaluation of a medicinal agent is giving way to the plan which calls for treating all patients, where possible, with the agent in question or with a placebo, the two being indistinguishable in physical form or appearance and their identity unknown to patient or investigator during the experiment.

HARRIS

Maren, T. H., Ash, V. I., and Bailey, E. M., Jr.: Carbonic Anhydrase Inhibition. II. A Method for Determination of Carbonic Anhydrase Inhibitors, Particularly of Diamox. Bull. Johns Hopkins Hosp. **95:** 244 (Nov.), 1954.

The principle of the method is as follows: CO_2 is bubbled at a constant rate through water containing indicator dye which changes color at pH 7. A standard amount of buffer (pH 9) is then added, changing the color of indicator. The hydration of CO_2 to H_2CO_3 neutralizes the added buffer and returns the indicator ot its original color. In the absence of carbonic anhydrase this hydration process requires 62–72 seconds. When enzyme is added, the reaction time is decreased with a reproducible relationship between reaction time and enzyme concentration. By keeping the amount of added enzyme constant, the reaction time becomes a measure of the concentration of carbonic anhydrase inhibitor present.

The method is sufficiently sensitive (0.5 microgram per gram tissue) and accurate ($\pm$10 per cent) for determination of Diamox in biological samples.

MCKUSICK

Miller, J. W. and Elliott, H. W.: Plasma Sympathin Concentrations of Dogs. Proc. Soc. Exper. Biology & Med. **87:** 487 (Nov.), 1954.

In Stage III of anesthesia, the plasma sympathin levels were reduced to about thirty per cent of the mean value for unanesthetized animals. The decrease in plasma sympathin during pentobarbital anesthesia could be explained by (a) a partial depletion of the adrenal gland of epinephrine and norepinephrine during induction, (b) a diminished central stimulation of the gland, or (c) a decreased production of the amines. The rapid disappearance of intravenous epinephrine from the plasma indicates that epinephrine was either (a) absorbed by tissues or red blood cells, (b) rapidly metabolized, or (c) excreted. Since the plasma level returned to normal after the initial rise following epinephrine administration, reversible storage by tissues seems unlikely.

BERNSTEIN

PHYSICAL SIGNS

Williams, C. and Soutter, L.: Pericardial Tamponade. Arch. Int. Med. **94:** 571 (Oct.), 1954.

Pericardial tamponade results when accumulation of fluid within the pericardial sac or constriction of the pericardium by scar or tumor tissue seriously interferes with the pumping action of the heart. It has been known for many years that the essential mechanical fault is restriction in diastolic filling when the pressure of fluid or constricting tissue prevents full expansion of the chambers during the resting phase of the cardiac cycle. A complex interrelationship of reduced cardiac output, altered venoauricular pressure gradients (from the encompassing fluid or scar), and the fluctuating intrathoracic pressure of respiration is productive of an important physical sign, called *pulsus paradoxus*. This term refers to the fall in cardiac output during inspiration, the fall being measured with the blood pressure cuff or by palpation of the pulse. It is not actually a paradoxic effect but is an accentuation of the normal fall in output during inspiration. The other important circulatory effect of acute tamponade is increased venous pressure, which frequently produces liver enlargement. Ankle edema and ascites are rarely seen.

Seventeen cases of pericardial tamponade are reviewed. The diagnosis was frequently missed owing to misconceptions about the syndrome of tamponade and because of failure to recognize the important physical signs—*pulsus paradoxicus* and pulsating neck veins. Dangers of acute tamponade are stressed. The procedures of pericardial tap and biopsy are discussed, and a section is devoted to the description of pleuropericardial "window." The use of all these procedures in diagnosis and treatment is outlined.

BERNSTEIN

PHYSIOLOGY

Sensenbach, W., Madison, L., Eisenberg, S. and Ochs, L.: The Cerebral Circulation and Metabolism in Hyperthyroidism and Myxedema. J. Clin. Invest. **33:** 1434 (Nov.), 1954.

Cerebral hemodynamic studies, using the nitrous oxide technic, were performed before and after treatment in 16 of 22 subjects with hyperthyroidism, and in 8 of 11 subjects with myxedema. The functional status of the thyroid gland was evaluated by clinical findings, BMR, I^{131} uptake, and serum protein-bound iodine.

Hyperthyroidism was accompanied by diminished cerebral vascular resistance and increased blood flow. Myxedema showed the reverse findings. When appropriate therapy resulted in euthyroidism, the cerebral circulation returned to normal. Oxygen and glucose consumption by the brain was not altered.

These changes are not specific to the thyroid hormone but rather reflect the variations in cardiac output and total peripheral resistance that accompanies states of altered thyroid function. In short, the rate of cerebral metabolism is uninfluenced by thyroid hormone.

WAIFE

Kao, F. F. and Ray, L. H.: Respiratory and Circulatory Responses of Anesthetized Dogs to Induced Muscular Work. Am. J. Physiol. **179:** 249, (Nov.), 1954.

During exercise under anesthesia (direct stimulation of hind leg muscles for 15 minutes) ventilation increased as a rectilinear function (directly proportional) of oxygen use. Both rate and tidal volume participated in the increase. The cardiac output increase was curvilinear (concavity downward) as a function of oxygen use. Increases in rate and stroke volume had a role. The arteriovenous oxygen difference was increased. Increases in ventilation were greater than those in output. This increased the ventilation-perfusion ratio.

OPPENHEIMER

Williams, M. H., Jr.: Relationships Between Pulmonary Artery Pressure and Blood Flow in the Dog Lung. Am. J. Physiol. **179:** 243, (Nov.), 1954.

Inflow and outflow pressures were measured and blood flow observed in the left lower lung of dogs. Pulmonary vascular resistance varies inversely with inflow pressure and flow. Pressure flow and resistance-flow curves were not changed by denervation of the bronchus or positive-pressure ventilation even though the latter increased resistance.

OPPENHEIMER

Gorlin, R. and Lewis, B. M.: Circulatory Adjustments to Hypoxia in Dogs. J. Appl. Physiol. **7:** 180 (Sept.), 1954.

This study correlates changes in blood pressure, blood flow and cardiac function with the duration and severity of hypoxia. Cardiac output, O_2 consumption, arterial O_2 saturation, femoral arterial, pulmonary arterial, and left arterial blood pressures were measured in 11 anaesthetized dogs during various grades of hypoxia. Vascular resistance and ventricular work were calculated.

The results were divided into 4 groups depending on the degree of hypoxia. In mild hypoxia (arterial O_2 saturation from 59 to 76 per cent) vasconstriction with a variable arterial hypertension was the only significant change. Moderate hypoxia (arterial O_2 saturation from 27 to 60 per cent) increased cardiac output, left ventricular work and arterial blood pressure. Tissue O_2 extraction and vascular resistance were diminished indicating systemic and pulmonary vasodilatation. Moderate hypoxia increases blood flow in order to maintain O_2 transport in spite of the decreased arterial O_2 content. Severe hypoxia

(arterial O_2 saturation 8 to 15 per cent) for 3.7 to 6.5 minutes increased cardiac output, left ventricular work, ventricular diastolic filling pressure and arterial blood pressure. There was a marked decrease in tissue O_2 extraction. Prolongation of severe hypoxia (average arterial O_2 saturation 12.5 per cent) for 10 minutes failed to increase cardiac output so that O_2 consumption decreased. Cardiac work was unable to increase enough to compensate for the low O_2 saturation so circulatory failure occurred.

O_2 consumption was maintained until protracted severe hypoxia caused circulatory failure. Increased left ventricular work could be maintained for long periods of time if arterial O_2 saturation was over 40 per cent and for short periods of time if this saturation was over 25 per cent.

WECHSLER

Meyer, J. S., Fang, H. C. and Brown, D. D.: Polarographic Study of Cerebral Collateral Circulation. Arch. of Neurol. and Psychiat. **72:** 296 (Sept.), 1954.

Multiple, simultaneous records of the oxygen availability of the cerebral cortex in monkeys and cats have been made by the polarographic method simultaneously with cortical thermoelectric records, the blood pressure record, and the EEG.

After occlusion of one or both carotid or vertebral arteries, the severity and duration of the ischemia of the cortex depends on the contribution of the anastomotic vessels.

Occlusion of the middle cerebral artery or of a small cerebral vessel is followed by a fall in the local oxygen availability in the distribution of the occluded vessel. There is also a bordering zone and an outer, anastomotic zone.

The area of ischemia is minimized by breathing pure oxygen and is increased by a fall in blood pressure. The collateral circulation is not improved by cervical sympathectomy, stellate ganglionectomy, or section of the seventh nerve roots, unless there is a coincident rise in blood pressure.

The maintenance of the systemic blood pressure at optimum levels and the administration of oxygen are the most potent aids to development of collateral circulation in the treatment of cerebral vascular occlusion. Sympathectomy does not appear to be of significant therapeutic value.

BERNSTEIN

Ahrens, E. H., Blankenhorn, D. H. and Tsaltas, T. T.: Effect on Human Serum Lipids of Substituting Plant for Animal Fat in Diet. Proc. Soc. Exper. Biol. & Med. **86:** 782 (Aug.–Sept.), 1954.

A well controlled study over a four-month period was done on a metabolic ward on six obese individuals of the effect of plant fat substitution for animal fat upon serum lipid level. Caloric intake was maintained and body weight remained constant. There was an approximate 20 per cent reduction in the concentration in the serum of free and esterified cholesterol and of phospholipids when plant fats were substituted for animal fats in the diet. There was no change in the level in the serum of neutral fats.

HARVEY

Parkins, W. M., Jensen, J. M. and Vars, H. M.: Brain Cooling in the Prevention of Brain Damage During Periods of Circulatory Occlusion in Dogs. Ann. Surg. **140:** 284 (Sept.), 1954.

Experiments were performed on dogs in which 2 polyvinyl catheters were placed in the carotid artery, one directed toward the heart and the other toward the brain. These were connected to a pump coil system which was capable of cooling the blood in the system. In this manner the brain alone could be cooled for varying periods of time.

It was shown that with the method, adequate central nervous system protection was produced against complete anoxia of 30 minutes duration.

ABRAMSON

Miller, W. F.: A Physiologic Evaluation of the Effects of Diaphragmatic Breathing Training in Patients with Chronic Pulmonary Emphysema. Am. J. Med. **17:** 471 (Oct.), 1954.

After evaluating pulmonary function data on 24 patients with chronic pulmonary emphysema studied before and after a six to eight week period of diaphragmatic breathing training, the author concludes that such training is an effective adjunct in the treatment of pulmonary emphysema and that such training can be expected in most instances to produce objective improvement in pulmonary function.

Increased diaphragmatic excursion, accomplished by this training, resulted in a striking increase in tidal volume at a lower respiratory rate and respiratory mid-position. More effective alveolar ventilation was accomplished without significant increase in total ventilation except in those instances in which it was decreased prior to training. Improved alveolar ventilation was indicated by increased oxygen removal rate, increased arterial oxygen saturation, decreased arterial pCO_2 and increased exercise tolerance with less dyspnea.

HARRIS

Glaviano, V. V.: Changes in Cardiac Output During the Transition From Closed to Open A-V Fistula in the Unanesthetized Dog. Am. J. Physiol. **179:** 268 (Nov.), 1954.

When a unilateral femoral A-V fistula is suddenly opened in a dog there is observed a tachycardia and increased stroke volume. These increases are very rapid in onset. Fall in systemic pressure due to an open A-V fistula produces cardiodynamic responses

from which an increase in output ensues. Atropine and vagotomy eliminate the tachycardia after acute A-V fistula.

OPPENHEIMER

Burch, G. E.: A Method for Measuring Venous Tone in Digital Veins of Intact Man. Arch. Int. Med. **94:** 724 (Nov.), 1954.

A digital plethysmographic method is described for observing variations in tone of the venous side of the vascular bed of intact man. Venous tone of the finger tip of patients with advanced chronic congestive heart failure was found to be elevated. The rates and volumes of inflow, outflow, and difference between inflow and outflow for the finger tip were reduced in the patients with chronic congestive heart failure. Simultaneously recorded curves of the time courses of rates and volumes of inflow and outflow and of the difference between the rates and volumes of inflow and outflow are illustrated, which, upon careful study, reveal many interesting physiologic aspects of digital inflow and outflow in congestive failure.

During the course of these experiments it was again observed that the systemic venous tone in all of the patients with chronic congestive heart failure was elevated considerably. It was suggested that the increase in venous tone was due in large part to a generalized increase in sympathetic venoconstrictor activity. The relationship of the elevated venous tone to the clinical manifestations of congestive heart failure is discussed. An accidental observation was that the intravenous administration of hexamethonium for purposes of experimentally reducing venous tone produced considerable to even dramatic improvement in the clinical symptoms and signs of advanced congestive failure; the degree of the improvement tended to be directly related to the degree of reduction in venous pressure, but the causative relationship of these two phenomena has not been determined.

BERNSTEIN

RHEUMATIC FEVER, RHEUMATIC HEART DISEASE, COLLAGEN DISEASES

Wang, P., Glass, H. L., Goldenberg, L., Stearns, G., Kelly, H. G. and Jackson, R. L.: Serum Vitamin A and Carotene Levels in Children with Rheumatic Fever. Am. J. Dis. Child. **87:** 659 (June), 1954.

The serum vitamin A level of rheumatic children is found to be decreased (a) during the acute and early subacute stages of the disease, (b) in patients with passive congestion of the liver, (c) during upper respiratory infections, (d) in patients with acute exacerbation of rheumatic processes, and (e) in those with an inadequate vitamin A and carotene intake of some duration. Corticotropin and cortisone profoundly affect the levels of serum vitamin A and carotene in different ways during the various stages of active rheumatic fever. Vitamin A, either in aqueous or oily medium, was well absorbed by children in varying stages of rheumatic fever.

BERNSTEIN

Greenstein, N. M.: Corticotropin in Rheumatic Carditis. Am. J. Dis. Child. **87:** 694 (June), 1954.

Twenty-eight children with an acute exacerbation of rheumatic fever were treated with 300 mg. per day of corticotropin, intramuscularly, for a period of 14 to 18 days. On cessation of therapy, no significant rebound phenomena or flare-up of rheumatic activity took place. Within 24 to 48 hours after the first injection of corticotropin, both right and left ventricles became markedly dilated. The heart lay on the underlying diaphragmatic surface like a sack of meal. The contractions were much less forceful than the previous tumultuous contractions and showed an undulating, almost accordion-like motion. These changes persisted throughout the entire course of treatment. Within 48 hours after the abrupt cessation of corticotropin, however, they disappeared rapidly, and the ventricular dilatation, "meal-sack" drooping, and accordion-like contractions could no longer be seen. A follow-up period of 12 to 30 months revealed no increase in the size of the various heart chambers, suggesting that progressive rheumatic activity had been checked or prevented.

BERNSTEIN

Shackman, N. H., Heffer, E. T. and Kroop, I. G.: The C-Reactive Protein Determination as a Measure of Rheumatic Activity. Am. Heart J. **48:** 599 (Oct.), 1954.

C-reactive protein determinations were performed on the sera of twenty-four patients in order to help determine the presence or absence of activity. Follow-up was done on these patients by the same group of pediatricians and cardiologists. X-ray films, fluoroscopy of the heart, and electrocardiograms were frequently made at the onset of the disease and on an average of once a month during convalescence. The white blood count, erythrocyte sedimentation rate, and plasma fibrinogen were done at least once a week. The cephalin-cholesterol flocculation, zinc turbidity, thymol turbidity, and gamma globulin precipitation tests were also done once a week. In this study, the absence of activity was judged by the complete and persistent subsidence of all clinical and laboratory manifestations of the disease.

There was a close correlation between the inactive state and a negative C-reactive protein determination. However, there were two instances of a negative C-reactive protein in the presence of rheumatic activity. A positive test in Syndenham's chorea should suggest the presence of an associated

carditis. The C-reactive protein determination was a better guide to activity than the sedimentation rate which showed protracted elevation despite the inactive state.

RINZLER

Kroop, I. G., Heffer, E. T. and Shackman, N. H.: An Evaluation of Electrophoresis in Rheumatic Fever. Am. Heart J. **48:** 612 (Oct.), 1954.

An analysis was made of 40 electrophoretic determinations of the serum proteins in 37 patients with rheumatic fever. Beta globulin elevation was encountered in seven out of thirty patients with rheumatic fever, whereas this fraction is rarely elevated in the postinfectious period of normal individuals (one out of 36 patients). Changes in the alpha-1, alpha-2 and gamma globulins were variable and nonspecific in rheumatic fever. A normal electrophoretic pattern may be obtained in the presence of rheumatic activity. It is concluded that electrophoresis is of little absolute value in determining rheumatic activity.

RINZLER

Wilson, J. K. and Greenwood, W. F.: The Natural History of Mitral Stenosis. Canad. M. A. J. **71:** 323 (Oct.), 1954.

One hundred seventy-one patients with mitral stenosis, seen from 1937 to 1941 in the public wards of the Toronto General Hospital, have been followed up to death or to the spring of 1953. Patients with tight mitral stenosis should be treated by commissurotomy as early after the appearance of symptoms of "severe pulmonary congestion" as possible. Survival rates indicate that 16 per cent of the patients died within six months after the appearance of severe pulmonary congestion. The risk of operation is in the vicinity of 6 per cent in similar cases. The average age onset of severe pulmonary congestion in this series was 40.1 years; 50 per cent of these patients were dead by the end of five years, and 80 per cent within 15 years. Pregnancy commonly precipitates severe pulmonary congestion. Approximately one-third of these patients died within ten years; one-third survived ten years but had severe disability; and one-third reverted to a benign stage of their disease. The evidence indicates that pregnancy per se has no delayed deleterious effect on the course of rheumatic heart disease. Right heart failure appeared, on the average, two years after the onset of pulmonary congestion. Twenty-four per cent of these patients were dead in six months, 50 per cent in three years, and 91 per cent in 15 years. Auricular fibrillation is evidence of advanced disease; the average age of onset was 43.3 years. Sixteen per cent were dead in six months, 50 per cent in five years, and 91 per cent in 15 years.

The best indications of the prognosis in a case are the heart size and functional capacity. Of the 65 per cent of the patients with a cardiothoracic ratio over 60 per cent, only 35 per cent were still alive in five years and 22 per cent in ten years.

BERNSTEIN

ROENTGENOLOGY

Wyman, S. N.: Angiocardiography. A Guide to Mediastinal Exploration. New England J. Med. **251:** 723–729 (Oct. 28), 1954.

This report is intended to emphasize the fact that, in many cases, it is possible to determine the nature of centrally located mediastinal or juxtacardiac shadows by means of angiocardiography and without thoracotomy, particularly to determine the relation of such shadows to the heart and great vessels. Much of the usefulness of the method of angiocardiography rests upon the demonstration of progressive degrees of opacification and the comparison of a number of successive films which may show quite subtle differences. These points are illustrated by a series of nine cases including instances of (a) pulmonary artery aneurysm, (b) absent left pulmonary artery, (c) dilated aberrant right subclavian artery lying between the esophagus and aorta, (d) coarctation of the aorta, (e) persistent left superior vena cava into which the pulmonary veins were emptying, (f) hypertrophic lymph nodes lying near the left cardiac border near the pulmonary artery, (g) an enlarged thymus in a child, and (h) a probable anomalous right subclavian artery in a patient with a small primary carcinoma of the upper cervical esophagus. The author points out that this method strengthens the case for mediastinal exploration in some patients and indicates that in others thoracotomy is unnecessary and possibly a dangerous procedure. Furthermore, in those cases in which thoracotomy is done, the surgeon is provided with additional valuable information regarding the vascular structures in the thorax prior to the exploration.

ROSENBAUM

Glaser, E. M., McPherson, D. R., Prior, K. M. and Charles, E.: Radiological Investigation of the Effects of Haemorrhage on the Lungs, Liver and Spleen, with Special Reference to the Storage of Blood in Man. Clin. Sc. **13:** 461 (Nov.), 1954.

There are contradictions in the literature regarding the question of blood storage in man, and the locations of blood stores if they do exist. In an effort to clarify the problem, the authors resorted to radiologic methods to study changes in lung vascularity and in the size of the liver and spleen after hemorrhage. Eight healthy young men were rapidly bled of 420 ml., and six subjects acted as controls. Rigidly standardized radiologic technics were used, the x-ray films of the chest and upper abdomen were made in triplicate and viewed by a radiologist who was completely unfamiliar with the conditions of the experiment. After bleeding, the size and number of lung vessels diminished in all subjects, and in seven sub-

jects, the size of the liver shadow. The results were statistically significant, whereas, in the controls, the changes were compatible with random distribution of spontaneous fluctuations. Changes in splenic outline approached, but did not achieve, statistical significance. The authors conclude that the lungs and liver are "blood-stores," and that the storage of blood in man may take place in macroscopic vessels.

ENSELBERG

Boyarsky, S.: Paraplegia Following Translumbar Aortography. J. A. M. A. **166:** 599 (Oct. 9), 1954.

Complete motor and sensory paralysis below the level of the eighth thoracic segment occurred in a patient after aortography with 70 per cent sodium acetrizoate (Urokon) for demonstration of a possible aortic aneurysm. The patient later regained sensory, bladder, and partial motor function. Two lessons can be learned from this case. One is that improvement in technique for aortography must be carried on unceasingly. Secondly, that aortography is not without some risk. The study therefore should not be done unless the information to be gained will influence the diagnosis, prognosis, or therapy enough to justify the risk. The probable cause of paralysis in this case was thrombosis of the anterior spinal artery or direct toxic action of the sodium acetrizoate on the spinal cord.

KITCHELL

Felson, B.: Translumbar Arteriography in Intrinsic Disease of the Abdominal Aorta and its Branches. Am. J. Roentgenol. **72:** 597 (Oct.), 1954.

From experience with over a thousand aortographies of the abdominal aorta, performed by the translumbar route, the author has arrived at the conclusion that this method yields valuable information with a high degree of safety. Definite information as to the presence and sites of thromboses and aneurysms can be determined; arteriovenous fistula can be demonstrated and the diagnosis of renal infarction can be made.

SCHWEDEL

Namin, P.: Percutaneous Vertebral Angiography. J. Neurosurg. **11:** 442 (Sept.), 1954.

The author believes that percutaneous vertebral arteriography can render numerous real services, sometimes irreplaceable, and that it is relatively benign, if one makes the injections gently.

The conclusions were based on 162 percutaneous vertebral angiographies made since 1948 in the Neurosurgical Clinic of the Pitie. The author describes the normal radiological anatomy. He also describes the most characteristic pathological aspects, insisting on the value of vertebral arteriography in the diagnosis of tumors in the region of the cerebello-pontine angle and of the clivus.

BERNSTEIN

Hyman, J. B. and Epstein, F. H.: A Study of the Correlation Between Roentgenographic and Post-Mortem Calcification of the Aorta. Am. Heart J. **48:** 540 (Oct.), 1954.

The accuracy of roentgen diagnosis of arteriosclerosis of the thoracic and abdominal aorta was correlated with post-mortem studies without knowledge of the individual radiologic report. Calcification of the thoracic aorta was diagnosed if a definite crescent-shaped density in the knob or a linear streak over one centimeter long in the descending portion of the aorta was visualized. A density of the aortic knob which was neither typical in shape or position was classified as questionable. Calcification of the abdominal aorta was diagnosed in the presence of either linear densities at least one centimeter in length, or multiple and sometimes parallel linear densities, or solid shadows, in an area parallel and anterior to the lumbar spine. Pathologically, only gross calcification was noted.

Roentgenologic demonstration of aortic calcification proved to be an accurate method for the diagnosis of atherosclerosis. It usually indicated an advanced degree.

Posteroanterior chest films were taken at a distance of 6 feet at one-twenty seconds of a second, using an average of 300 ma. and 70 kv. Lateral abdominal films were taken with a bucky grid at a distance of 40 inches, at 1½ seconds, using an average of 300 ma. and 78 kv., centering the tube at the level of the first and second lumbar spine.

RINZLER

SURGERY IN HEART AND VASCULAR SYSTEM

Rivier, J. L., Naef, A. P. and Mahaim, I.: Errors and Difficulties in the Indication for Mitral Commissurotomy. Acta. cardiol. **9:** 500 (Fasc. 5) (Nov.), 1954.

The indication to mitral commissurotomy is based on criteria derived from clinical, roentgenologic, electrocardiographic and hemodynamic data. In a limited number of cases these data may be contradictory and the evaluation for surgery may become difficult. In very exceptional cases the data may be misleading and lead to erroneous conclusions.

In a series of 40 cases the preoperative diagnosis based on these data was found correct at surgery in 37. In 2 cases in which clinical findings suggested predominant mitral stenosis, the x-ray and electrocardiogram were consistent with this diagnosis whereas the pulmonary wedge pressure curve suggested mitral regurgitation in one. At surgery mitral insufficiency was found in both without appreciable degree of stenosis. The remaining case was very unusual. There was a loud first and reduplicated second sound at apex, left auricular enlargement on x-ray, auricular fibrillation and right axis deviation

in the electrocardiogram, and pressure elevation in both the pulmonary artery and pulmonary capillaries. The only major expected sign of mitral stenosis which was absent was a diastolic murmur. At surgery left auricular pressure elevation was confirmed by direct measurement. However, the mitral valve was completely normal, without any deformation of the orifice, with normal subvalvular structures. In the absence of any evidence of an aortic lesion, of chronic pericarditis and of hypertension, the symptomatology of this unusual case is ascribed by the authors entirely to left ventricular failure of unknown etiology.

PICK

Biörk, G., Axen, O., Wulff, H. B., and Overbeck, W.: Evaluation of Various Methods of Examination in the Diagnosis and Indications to Surgery in Combined Mitral Lesions. Ztschr. Kreislaufforsch. **43:** 673 (Oct.), 1954.

Fifty cases of operated mitral valvular disease were reviewed as to the relative value of physical signs and laboratory methods in the diagnosis of mitral stenosis and/or mitral insufficiency. In 84 per cent of the cases the presence of mitral insufficiency was correctly diagnosed, or excluded, by using auscultation, ordinary x-ray study, the electrocardiogram and the ballistocardiogram. In the experience of the authors an apical systolic murmur, grade III–IV, in the absence of hypertension and aortic insufficiency, strongly suggests the presence of a dynamic mitral regurgitation. A vertical axis in the electrocardiogram and a small left ventricle on the other hand, rule against it. In 16 per cent the authors had to resort to cardiac catheterization and angiocardiography and the latter proved more reliable in the differential diagnosis of the two conditions. Reference is made to direct puncture of the left atrium, combined with selective angiocardiography, which in the future may provide the most reliable information in doubtful cases.

PICK

Denst, J., Edwards, A., Neubuerger, K. T. and Blount, S. G. Jr.: Biopsies of the Lung and Atrial Appendages in Mitral Stenosis: Correlation of Data from Cardiac Catheterization with Pulmonary Vascular Lesions. Am. Heart J. **48:** 506 (Oct.), 1954.

Lung biopsies from twenty-three patients with mitral stenosis who were studied by cardiac catheterization prior to mitral commissurotomy were examined histologically. A positive correlation existed between the degree of vascular alteration and the pulmonary arteriolar resistance and mean pulmonary arterial pressure in the more severe cases of pulmonary hypertension. The hemodynamic pattern varied considerably in patients who exhibit less severe vascular lesion. The pathologic findings in the majority of cases were prominent fibroelastic intimal thickenings of the muscular arteries and arterioles, and in 32 per cent the media appeared hypertrophic. Such pathologic findings were also found in autopsy specimens of the lungs of patients with mitral stenosis. The control patients in the young age group, who were free from pre-existing lung or heart disease, with one exception, showed only mild changes at most. The patients from 50 to 70 years of age with arteriosclerotic or hypertensive heart disease, but without primary lung disease, showed somewhat more advanced changes than those in the older patients who had no heart disease.

It was considered that surgery for mitral stenosis should not be denied the patient either on the basis of data obtained by cardiac catheterization or because of pulmonary vascular lesions, which are not usually severely obstructive although almost always present.

RINZLER

Higginson, J. and Pepler, W. J.: Fat Intake, Serum Cholesterol Concentration, and Atherosclerosis in the South African Bantu. Part II. Atherosclerosis and Coronary Artery Disease. J. Clin. Invest. **33:** 1366, (Oct.), 1954.

Several previous reports had noted the infrequency of coronary artery disease among certain African groups. A review of post mortem material at a non-European hospital in Johannesburg, South Africa, revealed a lower incidence of severe atherosclerosis than in Danish or American hospital populations. The population which this hospital serves is habituated to a low fat, high residue diet.

WAIFE

Malinow, M. R., Hojman, D. and Pellegrino, R.: Different Methods for the Experimental Production of Generalized Atherosclerosis in the Rat. Acta cardiol. **9:** 480 (Fasc. 5), (Nov.), 1954.

Contrary to previous experience, the authors were able to induce generalized atherosclerosis in rats by combined feeding of cholesterol or oil with induction of hypothyroidism or production of a perinephritis. Histologically, the lesions produced closely resembled those considered as characteristic of arteriosclerosis in other species of experimental animals and in men. The authors feel that some of the conditions under which atheromatosis was produced in these experiments are more comparable to conditions present in humans than experimental sclerosis produced by cholesterol feeding alone.

PICK

Gilfillan, R. S., and Berry, J. D.: Diagnosis and Surgical Treatment of Arteriosclerosis. Geriatrics **9:** 409 (Sept.), 1954.

The authors are concerned with two main types of changes in the peripheral vessels: (1) narrowing and irregularity produced by subintimal debris and

subsequent calcification, and, (2) thrombosis. The diagnosis of arteriosclerosis clinically is based on the absence or diminution of one or more peripheral arterial pulsations. A systolic bruit may be heard over the terminal aorta, iliac or femoral artery. Roentgenograms of the abdominal aorta or peripheral vessels may reveal flaky calcifications.

The treatment of acute arterial obstruction and chronic peripheral arterial insufficiency is discussed. The authors recommend immediate heparinization for acute arteriosclerotic obstruction. If surgery is contemplated, protamine can then be used to reverse the anticoagulant action of Heparin. Medical vasodilators (Priscoline, Papavarine, tetraethylammonium chloride) are of little use. Sympathectomy is probably contraindicated. Arteriography is not considered harmful and may reveal that the arteriosclerotic involvement of the peripheral vessel is such that thrombectomy will be difficult unless thromboendarterectomy is performed coincidentally.

The authors list the important conservative measures for patients with chronic arterial occlusion. They suggest that endarterectomy should be limited to those with a severe claudication in whom the peripheral tissues are in jeopardy or in whom tissue necrosis has already taken place. Candidates should not present signs of severe myocardial, cerebrovascular, or renal changes. The mortality for this procedure in their hands has been 7.8 per cent.

RINZLER

Landen, C. and Bayer, O.: Further Investigations Concerning Pulmonary Function Tests in Mitral Stenosis Before and Following Surgery. Ztschr. Kreislaufforsch. **43:** 651 (Sept.), 1954.

Spirographic data at rest and after exercise on 50 patients submitted to mitral surgery were compared with respective data recorded before surgery. This comparison revealed that in 70 per cent of the cases impairment of pulmonary function demonstrable at rest had completely disappeared after the operation and was of much lesser degree in the rest. In almost all the respiratory data revealed some improvement in the capacity to perform work of moderate degree. This was found 6 to 10 weeks after surgery and persisted, with 3 exceptions, over a period of one-half to two and one-half years. The authors emphasize the value of pulmonary function tests for the pre- and post-operative evaluation of patients with mitral disease.

PICK

Mudd, J. G., Inkley, J. J. and Hanlon, C. R.: Myocardial Ischemia During Mitral Commissurotomy. Am. J. Med. **17:** 330 (Sept.), 1954.

From an electrocardiographic study of thirty patients undergoing surgery for mitral stenosis the records of five patients with electrocardiographic evidence of myocardial ischemia during clamping of the left auricular appendage are presented. It was not definitely established whether these changes were due to direct pressure on the left coronary artery or to traction on the surrounding structures of such degree that the artery was secondarily constricted. In many cases it would appear due to direct pressure on the left coronary artery by the rotation of the clamp toward the right side of the patient in the hands of the first assistant. The authors stress the advisability of careful electrocardiographic observations during certain phases of the operation, since these changes indicative of ischemia may be a premonitory sign of impending ventricular fibrillation during mitral commissurotomy. Among the interesting electrocardiographic changes was the appearance of Q waves in conventional leads, simulating myocardial infarction but of transitory nature. This observation again raises questions concerning the significance of the Q wave.

HARRIS

Wade, O. L., Bishop, J. M. and Donald, K. W.: The Effect of Mitral Valvotomy on Cardio-Respiratory Function. Clin. Sc. **13:** 511 (Nov.), 1954.

Ten patients were studied before surgery and again six to nine months after operation. Clinical improvement was evident in all but two, both of whom had mitral insufficiency. There was little change in radiologic feature in the group, and no important electrocardiographic changes in most instances. In one case, in which resting and exercising pulmonary artery pressure was markedly reduced, a pre-operative pattern of right ventricular preponderance disappeared.

In general, profound changes in the direction of normality were demonstrated in those patients who showed clinical improvement. The most striking changes involved cardiac output and A-V oxygen differences. Changes in ventilation during exercise were equally striking. Pulmonary arterial pressures, however, remained elevated though usually somewhat reduced. Possibly a better correlation might have been found with "pulmonary capillary" pressures had they been measured in all the cases. Increased pulmonary arterial resistance was not always reversed, even in patients showing considerable reduction in "pulmonary capillary" pressures.

The slight reductions in pulmonary arterial pressures during exercise resulted in only slight reduction of right ventricular work. Indeed, as many patients are now capable of increased exertion without discomfort, the right ventricle may be performing much more work than before operation. It is possible that this may lead to further right ventricular hypertrophy and right heart failure. The authors point to the possible dangers of re-establishing an increased cardiac output and exercise tolerance after apparently irreversible pulmonary hypertension has occurred.

ENSELBERG

Johns, T. N. P. and Blalock, A.: Mitral Insufficiency: The Experimental Use of a Mobile Polyvinyl Sponge Prosthesis. Ann. Surg. **140:** 335 (Sept.), 1954.

The authors describe a method for placing a polyvinyl sponge prosthesis in the mitral valve orifice. The study was performed on 30 dogs, of which 20 survived the operation and were then sacrificed 4 to 10 months afterward. The purpose of the investigation is to determine the reaction of the heart to the prosthesis with the idea in mind that such a procedure could be applied to human subjects with mitral insufficiency. The prosthesis is suspended across the ventricular portion of the mitral valve orifice between the commissures and parallel to the opposing edges of the leaflets. Its ends are pulled through the myocardium at the apices of the two papillary muscles, and anchored to the epicardial surface of the heart. According to the authors, the prosthesis provides a baffle which deflected the blood stream out of the atrium at the proper time, i.e., during ventricular contraction, and also functions as a ball mechanism, moving back into the ventricle during diastole so as not to obstruct ventricular filling.

It is the authors' opinion that the results of the experiments justify the use of this method in patients with mitral insufficiency.

ABRAMSON

Julian, O. C., Dye, W. S. and Grove, W. J.: Selection of Patients for Mitral Commissurotomy in Relation to Clinical Results. Arch. Surg. **69:** 273 (Sept.), 1954.

The authors studied a series of 139 patients with mitral stenosis before and after commissurotomy, in order to attempt to establish criteria for future selection of cases. They point out that the presence of left heart enlargement, as a result of either significant aortic valvular disease or mitral insufficiency, was a poor prognostic sign. On the other hand, they place little credence on auscultatory evidence of mitral insufficiency, since in a high percentage of cases the existence of an apical systolic murmur was not associated with actual regurgitation, as determined at the time of surgery.

ABRAMSON

DeBakey, M. E., Creech, O., Jr. and Cooley, D. A.: Occlusive Disease of the Aorta and its Treatment by Resection and Homograft Replacement. Ann. Surg. **140:** 290 (Sept.), 1954.

The authors reported on the results of resection of the aortic bifurcation and replacement with a lyophilized aortic homograft in 22 patients with thrombo-obliterative disease of the aorta. The average age in the group was 49 years, with a range between 33 and 63 years. The average duration of symptoms for the patients with complete occlusion was four and a half years, and for the group with incomplete occlusion, two and a half years. Aortography was found of value in determining the degree of obstruction. Histologic examination of the specimens removed at the operation supported the view that the thrombotic process began in the common iliac arteries and in the region of the aortic bifurcation and involved more proximal segments by propagation.

Besides aortic homografts, homografts were also placed into the iliac bifurcation in four cases, in the external iliac artery in three, in the common femoral artery in two, and in the superficial femoral artery in one. Two deaths occurred. All but four of the remaining patients experienced striking improvement, with complete restoration of pulses in the lower extremities.

The authors conclude that the complete occlusive form of thrombo-obliterative disease, generally confined to the terminal aorta and bifurcation, was ideally suited for resection with homograft replacement. On the other hand, the partially occluded process, tending to be less localized, did not warrant such a surgical approach, particularly when associated with peripheral arteriosclerosis obliterans.

ABRAMSON

Culbertson, J. W., Bedell, G. N. and Ehrenhaft, J. L.: Management of Patients With Mitral Stenosis Before, During, and After Mitral Valvuloplasty. Arch. Int. Med. **94:** 718 (Nov.), 1954.

The authors discuss the medical management of patients with rheumatic mitral stenosis in a university hospital before, during, and after mitral valvuloplasty, on the basis of experience of 95 cardiotomies with an operative mortality rate of only 4.3 per cent. Preoperatively congestive heart failure is controlled, and the presence of rheumatic activity or infection is excluded. During the operation cardiac mechanism is monitored electrocardiographically and left atrial pressure pulse waves are recorded.

In the immediate postoperative period patients are watched carefully for evidence of failure of expansion of the left lung, myocardial decompensation, cardiac rhythm disturbance, and arterial embolism.

Except for incisional pain, the only troublesome last postoperative complication has been a 10% incidence of a brief, febrile intrathoracic disease process characterized by chest pain, tachycardia, malaise, and sometimes congestive heart failure. They believe this to be nonrheumatic and suggest that multiple small pulmonary infarcts and secondary pleuritis may be important factors.

BERNSTEIN

Madoff, I. N., Thompson, J. E. and Streider, J. W.: Embolization in the Surgery of Mitral Stenosis. Report of a Successful Aortic Saddle Embolectomy. New England J. Med. **251:** 730–733 (Oct 28), 1954.

The authors report two instances of saddle embolism of the aorta occurring in the period immediately after finger-fracture of the mitral valve for mitral stenosis. In one patient a successful embolectomy was performed thirty-four hours after the mitral valvular surgery. In one patient, the initial change was increasing apprehension and dyspnea whereas in the other it was progressive drowsiness. These general symptoms led to careful studies of the lower limbs and ultimate correct diagnosis of aortic embolization when the pulses, temperature and color of the legs were found to change. The careful evaluation of the peripheral pulses both before and after surgery is important in these patients. It is emphasized that embolectomy is the treatment of choice for aortic, iliac or femoral emboli but to be successful it must be carried out within eight to ten hours after the occurrence of the complication.

ROSENBAUM

Ellia, F. H., Jr., Kirklin, J. W., Parker, R. L., Burchell, H. B. and Wood, E. H.: Mitral Commissurotomy. Arch. Int. Med. **94:** 774 (Nov.), 1954.

This report concerns 131 patients with mitral stenosis who have undergone mitral commissurotomy. There were 11 hospital deaths, giving a mortality rate of 8.4 per cent. Of the patients surviving operation, 87.2 per cent either achieved an excellent result or were significantly improved. A significant factor influencing postoperative results with the anatomic status of the mitral valve. In only 6.6 per cent of patients with pliable valves was the operation a failure, while 43.2 per cent of those with scarred, immobile, often calcified valves either died subsequent to operation or were not improved.

Hemodynamic changes occurring during mitral commissurotomy include a decrease in left atrial and pulmonary artery pressure. Hemodynamic changes present three weeks after operation include a reduction in pulmonary arteriolar resistance and an increase in the ability of patients to increase their cardiac index on exercise. These changes persist in most instances and may become more marked a year or more after operation. The changes post commissurotomy, for various physiologic variables, give objective evidence which corroborates the functional improvement that these patients experience clinically.

BERNSTEIN

Muller, W. H., Jr. and Hyman, M.: Valvulotomy for the Surgical Relief of Aortic Stenosis. Surg., Gynec. & Obst. **99:** 587 (Nov.), 1954.

The authors discuss the selection of candidates for aortic valvulotomy, classification of patients with aortic stenosis, and contraindications to the operative procedure. In addition the surgical technique and problems encountered in treating this group of patients are discussed.

In selecting patients to undergo aortic valvulotomy, only those with a relatively pure aortic stenosis should be considered for operation by present technics. Many of these patients have a diastolic murmur representing some degree of insufficiency. However, if significant insufficiency is present, valvulotomy should not be performed. The diastolic pressure should be normal or only slightly diminished, and there should not be excessive left ventricle enlargement, which characteristically accompanies aortic insufficiency. Age is not necessarily a determining factor in the selection of patients for operation, but those older than 50 or 55 years should be considered carefully. Congenital aortic or subaortic stenosis should be operated upon when the diagnosis is carefully established. Finally calcification of the valve does not contraindicate operation.

The problems associated with aortic valvulotomy are considerably more complex than those encountered in treating mitral stenosis. A patient with aortic stenosis who is asymptomatic to any degree should be considered a candidate for operation because, unlike a patient with mitral stenosis, he may die of intractable acute heart failure, a relatively short time after the onset of symptoms. There is an additional problem regarding the surgical approach. One school advocates the retrograde approach on all patients with pure aortic stenosis. The other prefers the ventricular approach. There are advantages and disadvantages to both methods. The authors prefer the ventricular approach and report on thirteen cases in which aortic valvulotomies were performed. There was one operative death in a 63 year old patient who died while a retrograde approach through the innominate artery was being attempted.

The question of a dual stenotic lesion presents the problem as to which valve should be opened first. It is the authors' impression that the valve which seems to be most significantly affected should be opened first. For example, if the patient's primary symptoms have been angina and pounding, the aortic valve is opened first; whereas if pulmonary edema and dyspnea are present, the mitral takes precedence. One should carefully evaluate patients with severe mitral stenosis who are thought to have only minimal aortic stenosis, because relieving the mitral stenosis will greatly accentuate what may seem to be minimal aortic stenosis.

The complications which may arise from surgery are hemorrhage, ventricular fibrillation and acute heart failure. All these are imminent at the time of operation. In the immediate postoperative period an embolus, possibly from a calcified valve or from a thrombus in the ventricle or left auricle, is always a possibility. Reactivation of rheumatic fever may occur somewhat later. As to whether or not there will be recurrence of the stenosis, only time can tell. The authors do not believe that a heavily calcified valve is likely to reunite.

DENNISON

Hohf, R. P., Dye, W. S., Olwin, J. H. and Julian, O. C.: Low Thoracic-High Lumbar Sympathectomy for Vascular Diseases of the Legs. J. A. M. A. **156:** 1238 (Nov. 27), 1954.

The results of 60 operations on 47 patients were evaluated. Thirty-one of these were excisions of L-2 and L-3 ganglions and 29 were excisions of T-12 through L-3. In evaluating the effects of the low thoracic high lumbar sympathectomy, it is shown that results differ little from those of the usual lumbar sympathectomy. The higher sympathectomy permitted below-knee amputations in seven out of nine cases compared to one out of eight cases in the regular series. With this one exception the higher sympathectomy was of no greater benefit than the usual lower operation. Therefore, it is not recommended. It is suggested that future efforts to improve the results of sympathectomy should be directed toward interrupting the accessory pathways along the trunk.

KITCHELL

Turk, L. N. and Glenn, W. W. L.: Cardiac Arrest. Results of Attempted Cardiac Resuscitation in 42 Cases. New England J. Med. **251:** 795–803 (Nov. 11), 1954.

This report is concerned with 45 instances of cardiac arrest occurring in 44 patients over a period of 5 years at the Grace-New Haven Community Hospital. Cardiac massage was carried out with the chest open in all but four cases in which massage was performed from the abdominal cavity through the diaphragm. In one case the heart began beating spontaneously 36 seconds after the onset of arrest and in two patients the heart was found to be beating when the chest was opened. In one patient cardiac resuscitation was carried out on two separate occasions, 16 days apart. Arrest occurred 7 times in 260 cardiac surgical procedures and in other types of surgery the incidence was 1 in every 3000 cases. The authors considered the major factors responsible for sudden cardiac arrest in this series to be vagal stimulation, anoxia, hypercapnia and drug sensitivity. The importance of vagal-reflex inhibition of impulse formation at the sino-atrial node, probably potentiated by hypoxia and hypercapnia is emphasized. The vagal reflex influence of intubation, extubation and tracheal suction are mentioned as possible important precipitating causes of cardiac arrest. Ventricular fibrillation occurred as a primary arrhythmia only once in this series, although it developed during resuscitation in several others. Although defibrillation could almost always be accomplished, no patient with this disorder survived. The authors indicate that procaine or procaine amide are now used by them only when there is evidence of myocardial hyperirritability, since it is their impression that the arrested heart with normal irritability may be resuscitated more easily than one rendered unresponsive by these drugs.

ROSENBAUM

THROMBOEMBOLIC PHENOMENA

Andersen, A. R., Hansen, A. T., Husfeldt, E., Pedersen, A. and Thomsen, G.: Superior Caval Vein Syndrome. Three Cases Presumably Due to Thrombosis. One Case Treated by Anastomosing the Azygos Vein to the Right Auricle. Acta med. Scandinav. **150:** 81–94 (Fasc. 2) (Aug.), 1954.

The principal manifestations of the superior caval vein syndrome are reported to be dilatation of the veins of the head and neck, distention of the collateral veins of the thorax, cyanosis and edema of the face, dyspnea and pressure in the head, especially on exertion. If there is occlusion of the azygos vein, pleural exudate tends to occur, particularly on the right. The demonstration of an elevated venous pressure in the upper extremities together with a normal venous pressure in the lower extremities makes the diagnosis quite certain. Three cases are reported, one attributed to a blunt injury to the thorax with widespread hemorrhage, another due to a congenital deformity of the superior vena cava and the third following a febrile course and probable mediastinitis after a diphtheria vaccination. Venous angiocardiography, particularly when done electively by catheter, was especially helpful in localizing and delimiting the areas of thrombosis in all three cases. Thoracotomy was performed in two cases and in one of them, a child with a probable congenital anomaly of the superior vena cava, an anastomosis was created between the azygos vein and the right auricle with a good clinical response over a three-month follow-up period. It is believed by the authors that this is the first case on record in which surgical treatment has been carried out successfully.

ROSENBAUM

Clarke, E., Jones, N. C. H., and Logothetopovlos, J.: The Action of Tolazoline Hydrochloride on Cerebral Blood-flow in Cerebral Thrombosis. Lancet **2:** 567 (Sept. 18), 1954.

There was no consistent effect of this agent ("Priscol") on cerebral blood flow as measured by a modification of the Kety-Schmidt method in 14 patients with cerebral arteriosclerosis.

McKUSICK

Callow, A. D.: Insidious Thrombosis of the Aorta. Geriatrics **9:** 472 (Oct.), 1954.

The syndrome associated with slow, progressive thrombosis of the aorta at its bifurcation is called insidious thrombosis by the author. It is a commoner condition than has been formerly thought. The disease is characterized clinically by increasing fatigability and claudication of the lower extremities which extends into the buttocks. Low back pain is frequently present, impotence is common, and lower extremity arterial pulses are absent. Arteriosclerotic degeneration of the bifurcation of the aorta is the usual predisposing lesion. When

untreated, thrombosis may extend up the aorta to the renal arteries causing death from uremia or produce such severe ischemia of the lower extremities as to lead to gangrene. Lumbar sympathectomy is now recognized as an insufficient form of treatment. Thromboendarterectomy, when successful, has given satisfactory results. Increasing experience in vascular surgery has led to the perfection of a technic of resection of the aortic bifurcation and common iliac vessels with insertion of an arterial homograft. This procedure now appears to be the therapy of choice. Prolonged anticoagulant therapy which is necessary with thromboendarterectomy may not be necessary following aortic grafting. Long-term successful results of both thromboendarterectomy and resection of the involved segment and insertion of a homograft must still be awaited.

RINZLER

Warren, R., Linton, R. R. and Scannell, J. G.: Arterial Embolism. Ann. Surg. **140:** 311 (Sept.), 1954.

A study was made on 200 patients with a history of one or more arterial embolic episodes over a 17-year period of observation. The cases were divided into 2 groups: one consisting of embolic episodes occurring between 1937 and 1946 and the other, between 1947 and 1953. Only about 12 per cent of the emboli were in patients in whom no source was clinically evident. Approximately 76 per cent of the emboli were to limb arteries, about one-half being ocated in the lower extremities. The incidence of lembolism as a complication of mitral surgery was 16 per cent. Surgical treatment was undertaken in 47.7 per cent of cases in the later period (1947–1953) and 22.7 per cent in the earlier (1937–1946). A higher rate of limb survival was obtained in the former group.

ABRAMSON

Luke, J. C.: Thromboendarterectomy in the Treatment of Lower Aortic Occlusion. Arch. Surg. **69:** 205 (Aug.), 1954.

The author set up certain criteria to be utilized in selecting patients for surgical treatment of segmental occlusion of the lower portion of the aorta. The first was the presence of patency of the vessels distal to the bifurcation of the popliteal artery as determined by arteriography. Extensive arteriosclerotic involvement of the anterior and posterior tibial arteries and calcification of the aorta and common iliac arteries, as visualized by soft-tissue x-ray technic, were considered to be contraindications to operation. Most important in the final decision was the state of the heart and kidneys. Generally, patients more than 60 years of age were believed unsuitable for reparative surgery.

In the author's series, 8 patients were treated by thromboendarterectomy and 2 by excision of the occluded portion with replacement by homologous arterial grafts. It was his opinion that thromboendarterectomy was the procedure of choice in cases of segmental aortic and iliac occlusion.

ABRAMSON

Swank, R. L. and Dugger, G. S.: Fat Embolism; A Clinical and Experimental Study of Mechanisms Involved. Surg., Gynec. & Obst. **98:** 641 (June), 1954.

The authors presented 2 cases of fat embolism and then described the results of a study on rabbits in which fracture of the femur and muscle contusion were performed in an attempt to produce fat embolism experimentally. The results suggested that an important source of fat emboli is circulating fat globules which are held much of the time in the capillary bed of the general and pulmonary circulation. The authors presented the view that the circulating fat probably had its origin from the chylomicra. They believed that such states as shock and anesthesia relaxed the vascular bed, allowing the circulating fat, together with the fat from the fractured bones, to be washed through the pulmonary bed into the general circulation. The lodgment of this material in the vessels in the brain was considered to be the probable cause for the cerebral symptoms.

ABRAMSON

Towbin, A.: Pulmonary Embolism. J. A. M. A. **156:** 209 (Sept. 18), 1954.

Pulmonary embolism becomes an increasingly important problem as the extent of its incidence becomes unveiled. The study of vital statistics is not a good indicator of the incidence of pulmonary embolism because of inevitable errors in diagnosis and inadequate number of autopsies. Clinical surveys provide significant presumptive data regarding relative incidence of pulmonary embolism in hospital practice. Autopsy series study in general hospitals and in custodial institutions is important. Custodial institution studies provide unique information regarding the general incidence of terminal illness because the pattern of terminal illnesses in such an institution mostly parallels that in the general population. In 512 autopsies the author noted 132 cases with thromboembolic disease, or 25.7 per cent of the total. The study points out that pulmonary embolism has a far wider occurrence than is generally realized. It is one of the commonest direct causes of death in the aged. Its incidence will probably increase as it is primarily a disease of old age and the older age group is growing because many types of bacterial terminal illness are being controlled at present. Three clinical patterns are distinguished in cases of pulmonary embolism. First, sudden death, involving the major branches of the pulmonary arterial tree; a subacute form, with involvement of the large and medium sized pulmonary arteries; and a chronic clinical form usually incident to prolonged terminal illness in which only the small arteries are included. Three factors influencing the occurrence of pulmo-

nary embolism are age, sex and periods of enforced bed rest. The greater incidence in women than in men is unexplained. This study tends to dispel the supposition, deeply rooted in medical thinking, first, that pulmonary embolism is mainly a postoperative complication, and second, that it is a sudden and rapid form of death characteristically. The vast majority of these cases occurred in medical patients and only a small percentage died suddenly. As the clinical picture becomes recognized and as criteria for diagnosis becomes clarified, pulmonary embolism will be diagnosed more often and prophylactic and therapeutic measures will be pursued.

KITCHELL

Thomson, J. L. G.: Thrombosis of Major Cerebral Arteries. Brit. J. Radiol. **27:** 553 (Oct.), 1954.

Review of the clinical and roentgenographic features of twenty three cases of carotid artery thrombosis, seven cases of middle cerebral artery thrombosis, and one of posterior cerebral artery thrombosis. Cerebral arteriograms are often helpful in localizing the site of blockage.

SCHWEDEL

Johnson, J. K.: Ascending Thrombosis of Abdominal Aorta as a Fatal Complication of Leriche's Syndrome. Arch. Surg. **69:** 663 (Nov.), 1954.

A case of aortic bifurcation thrombosis is reported in which proximal and distal extension of the process occurred, as demonstrated at autopsy. According to the clinical story and the findings, the patient survived several episodes of mesenteric thrombosis, focal myocardial infarction, and a number of major operative procedures. Death was due to massive infarction of the kidneys, liver, spleen and bowel, with peritonitis from rupture of a gangrenous gall bladder.

The author called attention to the need for early diagnosis of aortic bifurcation thrombosis, at a time when adequate surgical intervention offers some hope of prolonging the life of patients with this disorder.

ABRAMSON

Innerfield, I.: Trypsin Given Intramuscularly in Chronic, Recurrent Thrombophlebitis. J. A. M. A. **156:** 1056 (Nov. 13), 1954.

Intramuscular trypsin has been observed to shorten the course of acute superficial or deep thrombophlebitis, enabling early ambulation and return to full activity. This study reports 18 patients with chronic thrombophlebitis of 2 to 9 years' duration in both men and women, ranging in age from 32 to 79 years. All these cases had had previous treatment with dicumarol or heparin but thrombi persisted for 2 to 9 years in spite of such therapy. After prolonged administration of a preparation of crystalline trypsin in oil (Parenzyme) the blood clots disappeared. On termination of trypsin therapy in 15 of the 18 cases thrombophlebitis again developed. This cleared with a short, intensive course of trypsin given intramuscularly and has not recurred since the patients have been given maintenance doses. Prior to trypsin therapy, seven patients had at least one episode of embolism and three had several. There have been no pulmonary emboli in these patients since treatment with trypsin was started. It is suggested that trypsin functions by activating an inadequate fibrinolytic system.

KITCHELL

VASCULAR DISEASE

Hoerner, E. F., Dasco, M. M., McKeown, J. and Case, H.: Altered Vasomotor Changes (Peripheral) in Hemiplegias. Angiology, **5:** 414 (Oct.), 1954.

Peripheral blood flow was evaluated in 43 hemiplegic and 9 normal individuals with the use of radioactive sodium (Na^{24}) according to the technics of Quimby and Smith and of Friedell. The authors state that increased blood flow was demonstrated in a group with flaccidity of the extremities and also in another group with diffuse cerebral involvement. A third group of patients 55 years of age also showed an increase in blood flow.

WESSLER

Leonard, F. C. and Nakib, A.: "Pack" Wiring of Aortic Aneurysm. Angiology **5:** 433 (Oct.), 1954.

A case is described in which, during wiring of a rupturing abdominal aortic aneurysm, the inserting wire ascended the aorta, passed through the aortic valve, and entered the left ventricle of the heart. There were no clinical evidences of this complication and the patient was relieved of the back pain of which he had originally complained.

WESSLER

Totten, H. P.: Peripheral arteriosclerosis. Clinical and Arteriographic Evaluation with Reference to Conservative Surgical Treatment. Angiology **5:** 355 (Oct.), 1954.

A program is outlined for successful conservative surgery in peripheral arteriosclerosis. The success of surgery is largely dependent on the integrity of the arteries below the bifurcation of the popliteal. Preoperative clinical and arteriographic examination will determine with a fair degree of accuracy the collateral blood flow potential of an extremity upon which the beneficial effect of sympathectomy is largely dependent. The benefits and limitations of lumbar sympathectomy are enumerated and the indications for and the results to be expected from thromboendarterectomy are discussed. Brief case reports with arteriograms are included to illustrate the various types and degrees of occlusion encountered in peripheral arteriosclerosis.

WESSLER

Shaw, E. W.: Avascular Necrosis of the Phalanges of the Hands (Thiemann's Disease). J. A. M. A. **156:** 711 (Oct. 16), 1954.

The author reports a group of cases of avascular necrosis of the phalanges of the hands, all in members of six generations of one family. This condition generally affects the proximal interphalangeal joints of the middle fingers of both hands, with less frequent involvement of the second, third and fourth fingers, and occasionally the fifth fingers. The changes are first noted in late childhood and during adolescence, the onset usually being insidious and at times associated with trauma or exposure to cold.

The condition is differentiated from rheumatoid arthritis by the absence of redness and heat in the involved joints and the lack of systemic symptoms. It differs from osteoarthritis because of the location of the pathologic alterations in the fingers and the early age of onset.

The pathogenesis consists of an osteochondritis of growing epiphyses, although the cause is unknown. The disorder results in very little incapacitation.

ABRAMSON

Bornstein, F. P.: Dissecting Aneurysm of the Thoracic Aorta Due to Trauma. Texas State J. Med. **50:** 720 (Oct.), 1954.

A case of a partial traumatic rupture of the aorta followed by a dissecting aneurysm is presented. From the autopsy and clinical findings, it can be established that this man suffered a tear in the intima and media at the time of accident and that a dissecting aneurysm developed in the following four hours. Upon rupture of this aneurysm, death occurred.

BERNSTEIN

Cranley, J. J., Herrmann, L. G. and Preuninger, R. M.: Natural History of Aneurysms of the Aorta. Arch. Surg. **69:** 185 (Aug.), 1954.

The authors reviewed the autospy protocols and clinical records is a large general hospital of all cases with pathologic diagnosis of aneurysm of the aorta. The over-all incidence of this condition was 1.4 per cent (221 cases). Syphilis was the etiologic factor in 189 patients, the lesions being located in the thoracic aorta in 89 per cent of the cases and in the abdominal aorta in 11 per cent. Of the 20 aneurysms in the abdomen, 2 were located below the renal arteries and the remainder above this level. Death was due to the aneurysm in at least 49 per cent of cases.

There were 32 aortic aneurysms due to arteriosclerosis. Of this number, 12 were located in the thoracic aorta and the remainder in the abdomial aorta. In 25 per cent of the cases, the aneurysm was the cause of death.

ABRAMSON

Matthews, J. D.: Vascular Disease in Diabetes Mellitus. Lancet **2:** 573 (Sept. 18), 1954.

A study was performed on 545 diabetic patients and 574 nondiabetic patients to determine the incidence of vascular disease. A greater prevalence was found in the former after the fifth decade. The vascular changes were commoner among those who required insulin, and increased with the duration of the diabetes. Retinopathy and albuminuria were much higher with poor than with fair control of the condition.

ABRAMSON

Menendez, C. V. and Linton, R. R.: Peripheral Vascular Diseases. New Eng. J. Med. **251:** 382–393 (Sept. 2), 432–438 (Sept. 9), 1954.

The authors summarize material published since 1949 from 331 publications concerning peripheral vascular disorders. Concerning peripheral arteriosclerosis they mention that lumbar sympathectomy is still the major therapeutic measure in the treatment of arterial insufficiency of the lower extremities. Since it was observed that ether anesthesia causes a fall in skin temperature of a previously sympathectomized limb, it is recommended that when bilateral, two-stage lumbar sympathectomy is performed, the second side should be done under some other anesthetic agent, such as spinal, rather than ether. The use of blood vessel grafts in peripheral arteriosclerosis is discussed at length and the authors think that the method is of value especially in the presence of short segmental areas of occlusion in the superficial femoral artery to relieve intermittent claudication and to save some extremities that otherwise would require amputation because of ischemic lesions of the feet and the lower leg. Arteriography is said to be adding to the knowledge regarding arterial disease in young patients and many presons previously considered to have Buerger's disease are now known to have peripheral arteriosclerosis. Lumbar sympathectomy together with cessation of smoking is considered the most effective treatment of thromboangiitis obliterans. Many types and technics of vascular transplants have been developed in recent years. The authors feel that it is too early to tell which type of grafts will stand the test of time without degenerative changes that may lead to obliteration or aneurysmal dilatation. It is thought that autogenous grafts are most likely to survive with least change since they remain as living tissue with some elastic and muscular tissue, whereas the homologous grafts are replaced by the host's connective tissue. Most workers report little benefit from therapeutic venous ligation in acute arterial occlusion but intermittent venous occlusion, properly administered, is considered valuable in an effort to save ischemic limbs in this disorder, when other methods such as vascular grafts are not possible.

The authors report observations from their own laboratory which disclosed that in several cases of Raynaud's disease the critical temperature, producing arteriolar spasm in each patient, was not significantly lowered by sympathetic block or sympathectomy. However, this does not negate the value of this procedure, for a drop in the vessel temperature to the critical level is more difficult to produce when the patient's peripheral vessels are constantly

maximally dilated and heated by the warm blood coursing through them. In the surgical management of Raynaud's disease it is recommended that a radical sympathectomy be done, including the inferior cervical and the first three dorsal ganglions and also the second and third spinal nerves within their roots in order to assure removal of the efferent pathways and to reduce the facility of regeneration to a minimum. To be adequate, it is said, the operation must produce a Horner syndrome. Linton's report concerning saddle embolectomy emphasizes six principles: early operation; direct and adequate exposure of the site of embolism; occlusion of the artery distal to the embolus before the artery is disturbed; avoidance of damage to the intima; and complete control of the arterial inflow both proximal and distal to the arteriotomy so that a meticulous intima-to-intima closure can be accomplished. The publications, concerning the management of aneurysms, are summarized by the statements that those of the abdominal aorta distal to the renal arteries, as well as those involving the iliac, femoral, popliteal, subclavian, brachial and carotid arteries, are treated best by extirpation of the aneurysm with restoration of the arterial continuity by the use of some type of blood-vessel graft. Aneurysms of the aortic arch, descending, thoracic and upper abdominal aorta may sometimes be partially resected, aortic continuity being maintained. Some aneurysms of the thoracic aorta are handled best by intrasaccular wiring, a method often giving good results with a relatively low operative mortality.

Disorders of the veins and lymphatics have been taken up in many publications. The most effective method of treating varicose veins appears to be stripping of the long and short saphenous systems, along with any accessory venous trunks. It is concluded that neither an anticoagulant nor ligation is the ideal prophylaxis or treatment for venous thrombosis; venous interruption, though not as effective, seems less dangerous than an anticoagulant. There are said to be few, if any, indications for lumbar sympathectomy in the treatment of the postphlebetic syndrome.

Portal hypertension is another condition which is reviewed at length. For active bleeding from esophageal varices which do not respond promptly to transfusion, a balloon tamponade is suggested, followed within several hours by transthoracic transesophageal ligation of the bleeding source. Selection of patients for portacaval or splenorenal anastomosis should include careful evaluation of the extent of any liver disease because those patients, with severely depleted hepatic function, present a grave operative risk.

Other conditions included in this review are vascular spasm, causalgia, frostbite, arteriovenous fistula and lymphedema.

ROSENBAUM

Hershey, S. G., Zweifach, B. W. and Metz, D. B.: An Evaluation of the Protective Action of Autonomic Agents in Peripheral Circulatory Stress. Anesthesiology **15:** 589 (Nov.), 1954.

The authors report observations of the actions of various autonomic drugs in protecting rats against experimentally induced stress situations.

Protection against drum trauma shock by significant prolongation of survival rate with premedication was shown for only three drugs: (1) S C 2159 (Searle), a ganglionic blocking drug; (2) dibenzyline, a predominantly adrenolytic drug, and (3) atropine, a predominantly anticholinergic drug. The protection did not appear to be related to the particular major autonomic blocking property of the drug. In hemorrhagic shock experiments, pretreatment with the same drugs also showed similar protective phenomena. In the latter experiments, the protection was not a function of the increased tissue blood flow created by autonomic blockade. It is suggested that true pharmacologic protection in stress is probably a function of a combination of the properties of the protective drugs, including changes induced at the cellular metabolic level.

SAGALL

Goldner, M. G., Loewe, L., Lasser, R. and Stern, I.: Effect of Caloric Restriction on Cholesterol Atherogenesis in the Rabbit. Proc. Soc. Exper. Biol. & Med. **87:** 105 (Oct.), 1954.

A controlled study was performed on rabbits to determine the effect, if any, caloric restriction had on the pathogenesis of atherosclerosis in rabbits. Two groups of rabbits were fed a standard diet with cholesterol added but in the one group the caloric value was approximately half that in the other group. Cholesterol, lipoprotein, and phospholipid levels in the blood were measured over a period of time; when the animals were sacrificed, the aortas were carefully examined and the atheromatous changes carefully graded. Rabbits on the severe caloric restriction showed statistically significant higher levels of cholesterol, phospholipid, and lipoproteins than the controls. The atheromatous changes in the aortas were greater in these underfed animals than in the control group.

HARVEY

Cannon, J. A. and Barker, W. F.: Indications for Vein Interruption in Treatment of Venous Thrombosis. Geriatrics **9:** 507 (Nov.), 1954.

Experience with 62 cases of pulmonary embolism secondary to venous thrombosis have led to the following conclusions: Anticoagulant therapy alone is inadequate; vein interruption and complimentary anticoagulant therapy are strongly recommended. The vein interruption should be performed at a level above the clotting process, but at the same time, as many normal, major venous return channels as possible should be spared.

RINZLER

AMERICAN HEART ASSOCIATION, INC.

44 East 23rd Street, New York 10, N. Y.

Telephone Gramercy 7-9170

RECORD NUMBER OF PAPERS SUBMITTED FOR AHA SCIENTIFIC SESSIONS

Close to 350 papers have been submitted for possible presentation at the 28th Scientific Sessions of the Association in New Orleans. This represents an increase of more than 100% over any previous year, an indication of the greatly heightened interest in the Sessions among physicians and research investigators throughout the country.

The Sessions are being held as part of the Association's 31st Annual Meeting, October 22–28.

Proceedings in Circulation

Although time will not permit presentation of more than one quarter to one third of the papers, arrangements have been made to publish the abstracts of most of the papers in the October issue of *Circulation*. This issue will contain a special section including the program of the Annual Meeting and Scientific Sessions, as well as the abstracts. The section will be reprinted for distribution in New Orleans.

The Scientific Sessions and the programs of the Council on Community Service and Education and of the Council on Rheumatic Fever and Congenital Heart Disease will be conducted at the New Orleans Municipal Auditorium. Other events, including the annual meeting of the Assembly, top governing body of the Association, the AHA Annual Dinner and the Staff Conference of Heart Associations will be held at the Jung Hotel.

Scientific Sessions

Included on the scientific program will be general morning sessions and concurrent afternoon sessions of specialized interest to members of the various sections and councils of the Heart Association including the Sections on Clinical Cardiology, Cardiovascular Surgery, Circulation and Basic Science (jointly), the Council for High Blood Pressure Research and the Council on Rheumatic Fever and Congenital Heart Disease. The program is being drawn up by a committee under the chairmanship of Clarence de la Chapelle, M.D., New York, and the co-chairmanship of George Burch, M.D., New Orleans.

Joint Program Planned

A program under the joint auspices of the Council on Rheumatic Fever and Congenital Heart Disease and the Council on Community Service and Education will be devoted to discussions of rheumatic fever prevention and the problems of cardiac children in the schools. Among the participants in these discussions will be Leona Baumgartner, M.D., Commissioner of Health of New York City; S. Gilbert Blount, M.D., Denver; Edward E. Fischel,

The Schedule

Here, in brief, is a schedule of events for the Annual Meeting and Scientific Sessions:

Scientific Sessions: October 22–24, Municipal Auditorium.

Community Service and Education Program: October 23, Auditorium.

AHA Annual Dinner: October 23, Jung Hotel.

Joint Program, Councils on Community Service and Education and Rheumatic Fever and Congenital Heart Disease: October 24, Auditorium.

Assembly Panels: October 25, Jung Hotel.

Assembly Luncheon: October 25, Jung Hotel.

Assembly Annual Meeting: October 26, Jung Hotel.

Staff Conference of Heart Associations: October 26, 27, Jung Hotel.

Staff Conference Workshops: October 27, 28, Jung Hotel.

M.D., New York; Miss Anna Kalmanowitz, Boston; Gene Stollerman, M.D., Chicago; and Lewis Wannamaker, M.D., Minneapolis. Bernard Walsh, M.D., Washington, D. C., is Chairman of the Program Committee.

Community Service Programs

The Community Service and Education Council is also planning a separate program on Body Weight and Heart Disease and on Rehabilitation. Harold Feil, M.D., Cleveland, Chairman of the Program Committee, has announced that participants will include Martin Goldner, M.D., New York; Grace A. Goldsmith, M.D., New Orleans; Herman K. Hellerstein, M.D., Cleveland; E. A. Irvin, M.D., Dearborn, Mich.; Dr. Doris Johnson, New Haven; Herbert H. Marks, New York; Herbert Pollack, M.D., New York; W. Henry Sebrell, M.D., Director of the National Institutes of Health, Bethesda, Md.; John Goodrich Smith, M.D., Rocky Mount, N. C.; and Paul D. White, M.D., Boston.

Special Lectures

Two special lectures have been scheduled. The Lewis A. Conner Memorial Lecture on Saturday, October 22, and the George E. Brown Memorial Lecture on Sunday, October 23. The Conner Lecture will be presented by George Perera, M.D., Associate Professor of Medicine at the Columbia University College of Physicians and Surgeons. His subject will be *Primary Hypertension*. George Burch, M.D., Henderson Professor of Medicine at the Tulane University School of Medicine, will give the Brown Lecture on the subject of *Digital Rheo-Plethysmography*.

Exhibits

For the first time, a wide range of commercial and scientific exhibits will be featured at the Association's Scientific Sessions. These exhibits will be set up at the Municipal Auditorium.

Non-Members Welcome

Attendance at the Scientific Sessions is open to non-members as well as to Heart Association members. A moderate registration fee of $3.00 will be charged to non-members. This fee will entitle them to copies of the printed proceedings. Medical students, internes, residents, research workers and nurses will be welcome without payment of the fee. Registration forms, which contain provisions for reserving hotel accommodations, can be obtained from local Heart Associations and from the AHA, 44 East 23 Street, New York 10, N. Y.

Mexican Tour

An 8-day medical tour to Mexico has been arranged to follow the Annual Meeting. Starting from New Orleans on Thursday, October 27, the tour will include special scientific programs in Mexico City arranged by the National Institute of Cardiology. These programs will be offered on the mornings of October 31, November 1 and November 2. The itinerary will also include visits to points of religious, cultural and recreational interest in the Mexico City area. Approximate cost of the tour will be $200, including transportation, hotel and several meals.

In addition, an optional tour to the Pacific Coast resort of Acapulco has been arranged from Thursday, November 3 through Saturday, November 5. Additional details and reservations can be obtained from the Medical Division of the Association.

NOVEMBER 1 IS DEADLINE FOR GRANT APPLICATION

November 1 is the deadline for applying for grants-in-aid to be awarded by the Association in support of cardiovascular research during the fiscal year beginning next July 1. Full information and application blanks can be obtained from the Medical Director of the Association. Applications for Association research investigatorships and fellowships for the same period had to be submitted by September 15.

HIGH BLOOD PRESSURE COUNCIL MEETS IN CLEVELAND, NOV. 18–19

The 1955 annual meeting of the Association's Council for High Blood Pressure Research has been scheduled for November 18 and 19 in Cleveland. Attendance is by invitation.

1954 BLOOD PRESSURE COUNCIL PROCEEDINGS NOW AVAILABLE

Proceedings of the 1954 Annual Meeting of the Association's Council for High Blood Pressure Research have now been published in book form, and copies are available from the Association.

The 140-page volume includes the symposia and panels on Nerve Transmission, Muscle Metabolism and Problems of Retirement.

Among the medical scientists who contributed to the sessions are John H. Green, Victor Lorber, Amedeo S. Marrazzi, Wilfried F. H. M. Mommaerts and Albert Szent-Gyorgyi.

Cost of the proceedings is $2.50. For those who wish copies of the proceedings of the 1952 and 1953 meetings of the Council, as well as the 1954 proceedings, a combined price of $4.00 for all three has been set. Address requests to Medical Division, American Heart Association, 44 East 23 Street, New York 10.

STUDY TO INVESTIGATE RELATION OF EXERTION TO HEART DISEASE

The relationship between work and exercise and heart disease, long a problem to the medical profession as well as to employers and workers, will be the subject of a study to be conducted under the supervision and with the support of the Association. Milton Helpern, M.D., New York, and Myron Texon, M.D., New York have accepted appointment as responsible investigators for the project. They will be assisted by Sidney Weinberg, M.D., pathologist and research associate, and by several clinical and laboratory scientists.

The project will be under the jurisdiction of the Association's Committee on the Effect of Strain and Trauma on the Heart and Great Vessels. A grant of $13,750 has been approved by the Board of Directors to finance the investigation.

Another aspect of the strain and trauma question with relationship to cardiovascular disease is also to come under study by the Association within the next few months. A project is being organized which will have as its purpose the critical analysis of legal decisions concerning cardiovascular cases and the relation to workmen's compensation law and practice.

HEART SOUND TAPE LIBRARY ESTABLISHED BY ASSOCIATION

A library of tape-recorded heart sounds and murmurs has been established by the Association for use in undergraduate and post-graduate medical education. The Association's Committee on Auscultatory Phenomena has approved inclusion of 10 teaching reels and 34 different heart sounds and murmurs available in loop form at two different speeds, 1⅞ inches per second and 7½ inches per second.

The tapes, information on their use and descriptive materials on their content will be available shortly from the Medical Division, American Heart Association, 44 East 23 Street, New York 10.

REGISTRY OF CARDIOVASCULAR PATHOLOGY

A unique collaboration between pathologists of this country and the Armed Forces Institute of Pathology is the development and operation of the various registries of pathology. In addition to providing mutual benefit to the pathologist and the Institute, the registries provide American medicine with a source of pathological information and materials for study. Recognizing the need for such a source in the field of cardiovascular diseases, the Armed Forces Institute of Pathology in 1948 established the Registry of Cardiovascular Pathology, sponsored in part by the American Heart Association.

The Registry of Cardiovascular Pathology prepares, studies, and catalogues all cardiovascular pathology received by the Institute. Materials are accumulated by the Armed Forces Institute of Pathology from military and veterans' services and from civilian sources. Since the establishment of the Registry, over 1300 disease entities have been studied and indexed. To date most of the materials submitted have been limited to four major groups, namely: neoplasms, congenital malformations, collagen disease, and endocarditis. However, there is a need for case histories and materials from the more common types of cardiovascular disease.

Utilization of the materials provided by the Registry has resulted in many comprehensive

studies of various cardiovascular diseases. In the past seven years, fifteen original publications dealing with these studies have appeared in the medical literature. Through the Registry, opportunities to study a large number of specific cardiovascular entities are afforded the physician interested in this field of medicine.

Part of the service of the Registries is to provide educational materials for physicians on a loan basis. Such a series of materials including microscopic slide sets, projection slides and monographs dealing with cardiovascular pathology are in preparation.

Any pathologist or physician may submit specimens from cases of cardiovascular disease to the Registry of Cardiovascular Pathology, Washington 25, D. C. For the most benefit in teaching and research, abstracts of case histories, pertinent laboratory data, electrocardiograms, and X-rays should be submitted with the specimens. (The original electrocardiograms and X-rays will be returned to the contributor after copies have been made.) The pathologist or the physician through his local pathologist may request opinions as to the pathological diagnosis of a specimen at the time it is submitted. Once the specimen is received by the Registry, it will be constantly available to pathologists, surgeons, and physicians in postgraduate training for personal study, research, and teaching.

The specimen may be restudied at any time by the contributor or, at his request, may be returned to him.

The Registry provides a valuable service to American medicine not only by providing a source for pathological materials which might be lost for lack of appropriate storage facilities, but also provides the physicians with the opportunity for study and research in the field of cardiovascular disease. The program of the Registry of Cardiovascular Pathology is beneficial to medical education in general, but, more specifically, many benefits are derived by the physicians who support the Registry by contribution of materials.

WASHINGTON STATE SYMPOSIUM

The Seventh Annual Symposium on Heart Disease will be held jointly by the Washington State Heart Association and the Washington State Department of Health at the University of Washington Medical School, Seattle, on September 30 and October 1. The themes will be "Myocardial Infarction" and "Pericarditis." The Symposium is the equivalent of nine hours of formal graduate training for members of the Academy of General Practice.

NEW YORK HEART FELLOWSHIPS

The New York Heart Association will offer this fall three Senior Fellowships, each for a period of three years and renewable for an additional two years, with annual stipends starting at $6000, and annual increments of $500. These fellowships are full time and are available to young men and women under the age of 35 who have attained a doctorate degree and demonstrated a competence for research, and who have a definite orientation towards fundamental research in the cardiovascular field. Research programs are to be carried out in recognized institutions in New York City.

For further information write the Medical Director, The New York Heart Association, Inc., 485 Fifth Avenue, New York 17. Closing date for applications is October 31, 1955.

MEETINGS CALENDAR

Sept. 19–22: American Hospital Assoc., Atlantic City, N. J. Edwin L. Crosby, 18 E. Division St., Chicago 10.

Sept. 20–23: American Roentgen Ray Society, Chicago. Barton R. Young, Germantown Hospital, Philadelphia 44.

Oct. 10: College of American Pathologists, Chicago. Arthur H. Dearing, 203 N. Wabash Ave., Chicago.

Oct. 22–28: American Heart Association, 31st Annual Meeting and 28th Scientific Sessions, New Orleans. American Heart Association, 44 E. 23rd Street, New York 10.

Oct. 24–26: American College of Gastroenterology, Chicago. Joseph Shaiken, 33 W. 60th St., New York 23.

Oct. 27–29: American Association for Surgery of Trauma, Chicago. James K. Stack, 700 N. Michigan Blvd., Chicago 11.

Oct. 27–29: Gerontological Society, Baltimore. Nathan W. Shock, Baltimore City Hospitals, Baltimore, Md.

Oct. 29–Nov. 3: American Society of Anesthesiologists, Boston. J. E. Remlinger, Jr., 188 W. Randolph St., Chicago 1.

Oct. 31–Nov. 4: American College of Surgeons, Chicago. Michael L. Mason, 40 E. Erie St., Chicago 11.

Nov. 1–3: International Enzyme Symposium, Detroit. Clarence E. Rupe, M.D., Secretary, Henry Ford Hospital, Detroit 2.

Nov. 9–13: International Symposium on Tuberculosis in Infancy and Childhood, Denver. Leonard S. Smith, Director of Public Relations, 3800 E. Colfax Ave., Denver 6, Colo.

Nov. 14–17: Congress of International Society for Research in Anesthesia, Boca Raton, Fla. Dr. R. J. Whitacre, 13951 Terrace Rd., Cleveland 12.

Nov. 14–18: American Public Health Assoc., Kansas City, Mo. R. M. Atwater, 1790 Broadway, New York 19.

ABROAD

Sept. 20–24: International Congress of the European Society of Haemotology, Freiburg, Germany. Prof. Dr. Ludwig Heilmeyer, Hugstetter Strasse 55, Freiburg, Germany.

Sept. 20–26: Assembly of the World Medical Association, Vienna, Austria. Dr. Louis H. Bauer, 345 East 46 St., New York 17.

Oct. 13–15: Annual Meeting of Canadian Physiological Society, London, Ontario. Dr. J. M. R. Beveridge, Department of Biochemistry, Queen's University, Kingston, Ontario, Canada.

Oct. 28–29: International Congress of Bronchoesophagology, Buenos Aires. Dr. Juan Carlos Arawz, Cangallo 4015, Buenos Aires, Argentina.

Nov. 6–13: International Congress of Allergology, Rio de Janeiro. Dr. Bernard N. Halpern, 197 Boulevard St. Germain, Paris 7.

Nov. 7–12: International General Medical Congress, Rosario, Argentina. Dean Jose Imhoff, Santa Fe 3100, Rosario, Argentina.

AMERICAN SOCIETY FOR THE STUDY OF ARTERIOSCLEROSIS

PROGRAM AND PROCEEDINGS OF THE NINTH ANNUAL MEETING AT THE SHERATON HOTEL, CHICAGO, ILL., NOVEMBER 5 AND 6, 1955

(All papers except the Addresses will be limited to 15 minutes for presentation plus 5 minutes for discussion)

SUNDAY MORNING NOVEMBER 5, 1955

Louis N. Katz, Presiding

8:15

Registration

9:00

1. Persistent Atherosclerosis in Patients under Treatment for Hypertension; Association with Serum Protein Concentration

Harriet P. Dustan, Lena A. Lewis, Irvine H. Page and A. C. Corcoran. From the Research Division of the Cleveland Clinic Foundation and the Frank E. Bunts Education Institute, Cleveland, O.

Treatment of hypertensive vascular disease with modern antipressor drugs permits evaluation of their effect on survival, of the relation between precedent hypertension and subsequent atherosclerosis and of the relationships between atherosclerosis and serum protein and lipoprotein concentrations.

Of a group of 96 patients followed from one and one half to four years, 82 suffered from essential hypertension of varying severity which entered the malignant phase in 41, while 14 had primary renal hypertension which was "malignant" in 8.

Among the 49 with "malignant" hypertension, 29 survived beyond the first year. This rate is double that found in untreated patients by Keith and Wagener. Of these, 4 died in the second and only 2 in the third year. Causes of death were evenly distributed between atherosclerosis, chronic renal failure and pulmonary fibrosis complicating the use of hexamethonium. Among the 41 with "nonmalignant" essential hypertension, 9 died of atherosclerosis and 1 of uncontrolled "malignant" hypertension.

Deaths attributable to atherosclerosis occurred in patients whose blood pressure levels were considered satisfactory and who showed regression of the usual signs of advancing hypertensive vascular disease. Thus, the data show a dissociation between blood pressure levels and atherosclerosis, but an association between prior severe hypertension and residual or progressive atherosclerotic complications.

The sera of patients with malignant hypertension usually showed abnormalities consisting of decreases in α-2 and increases in β globulin fractions with, in some, increases in γ also. These abnormalities tend to revert towards normal in survivors. Serum lipoproteins varied widely and less consistently than serum globulins in all groups. The data indicate a relationship between the incidence of atherosclerotic complications of prior hypertension and persistence of abnormalities in distribution of serum globulins.

9:20

2. Chronic Sodium Chloride Toxicity. The Arteriosclerotic Lesion

George R. Meneely, Janet Lemly-Stone, Robert G. Tucker, Thomas M. Blake, Stewart H. Auerbach, William J. Darby and Ernest W. Goodpasture. From the Research Laboratory, the Radioisotope Unit and the Medical and Laboratory Services of Thayer Veterans Administration Hospital and the Departments of Medicine, Biochemistry and Pathology of Vanderbilt University School of Medicine, Nashville, Tenn.

Rats were fed varying levels of increased sodium chloride as the sole variable in a purified diet con-

taining all known essential nutrients. Distilled water was provided ad libitum. In a small percentage (15 per cent) of rats eating high levels of NaCl a nephrosis-like syndrome occurred. Among the remainder life span was shortened, hypertension developed; there was a disturbance of lipid metabolism, renal and heart failure occurred, all in proportion to the amount of NaCl in the diet. The spectrum of hypertensive cardiovascular renal disease seen in the human was reproduced, ranging from a clinical course resembling that of mild "benign-essential" hypertension with minimal shortening of life span to rapidly progressive and lethal "malignant" hypertension. Arteriolar lesions occurred in incidence, extent and degree proportional to the increase in dietary sodium chloride and to the severity of the clinical course. In the more advanced disease, the renal arterioles were uniformly involved. Stainable lipid formed vacuoles in smooth muscle cells, some of which were necrotic. In many arterioles the elastic lamina was greatly swollen, frayed and intensely eosinophilic. The lumina were narrowed or even occluded. Visceral arteriolar lesions were fairly constant among these animals and were almost invariably present in the heart, pancreas, testis and gastrointestinal tract. In the less severe forms of the disease, the vascular lesion, both renal and general visceral, was less impressive and less constant, usually consisting of medial hypertrophy.

Increasing the potassium content of diets containing increased sodium chloride (bringing the sodium-potassium ration toward normal) abolished the occurrence of the nephrosis-like syndrome, resulted in decreased incidence and severity of hypertension, increased life span toward that of the control animals and diminished the extent and degree of changes produced by unbalanced increase of NaCl.

9: 40

3. The Effects of Dietary Sodium Chloride and Water in Young Rats Upon Cholesterol Induced Atherosclerosis

Campbell Moses, Joseph B. Boatman, Joseph Sunder and Grant Doering. From the Addison H. Gibson Laboratory, University of Pittsburgh School of Medicine, Pittsburgh, Pa.

Groups of young, male, singly caged rats were fed a diet for 90 days containing 0, 1.5, 4.5 or 13.5 per cent sodium chloride; they had unlimited access to demineralized drinking water. Two similar groups on a salt-free diet were supplied 1.5 or 4.5 per cent sodium chloride in their ad libitum drinking water. Water consumption in these animals was measured daily and food consumption three times weekly. During the control period and at 30, 60, and 90 days after beginning the sodium chloride regimen, 6 animals from each group were studied for total water, potassium and sodium consumption and output in urine and feces. The rate of Na^{24} excretion following intraperitoneal administration was also determined. At 90 days, representative animals from each group were sacrificed and serum and organ samples obtained.

One third of the remaining animals were continued on the same sodium chloride intake but also received 4 per cent dietary cholesterol, one third were returned to a normal diet plus 4 per cent cholesterol and one third remained on the high salt diet without any added cholesterol. At varying intervals after the initiation of cholesterol feeding representative animals were sacrificed for study. The variations in electrolyte balance, serum cholesterol, lipoprotein partition and vascular lesions will be discussed.

10: 00

4. The Effects of Uremia, Hypertension, and Dietary Fat On Arteriosclerosis in the Rat

Louis Tobian, Eleanor Dulit, and Carolyn Miller. From the Department of Medicine, University of Minnesota School of Medicine, Minneapolis, Minn.

All the rats in this study had one kidney compressed with a figure-of-eight ligature and the other kidney excised. Subsequently, certain rats developed hypertension and/or uremia. Of 21 such hypertensive rats on a diet containing 4 per cent fat, not one developed arteriosclerosis, while of 17 on a diet with 15 per cent fat, 6 developed arteriosclerosis, an incidence of 35 per cent. This association of arteriosclerosis with the level of dietary fat is not necessarily a "cause and effect" relationship.

Twelve of these hypertensive rats were on an identical diet containing 15 per cent fat. Six developed arteriosclerosis and 6 did not. All 6 rats with arteriosclerosis had a blood urea nitrogen above 95 mg. per cent; the 6 rats without arteriosclerosis all had a BUN below 95 mg. per cent. The data strongly suggest that uremia predisposes to this type of arteriosclerosis. On the high fat diet, five other rats which had undergone the usual kidney operations remained normotensive. Not one of these normotensive rats developed arteriosclerosis, not even the one severely uremic normotensive rat with a BUN of 119 mg. per cent. This was the only rat with a BUN above 95 mg. per cent that did not develop arteriosclerosis; it was also the only rat with a high BUN which did not have hypertension.

10: 20

5. Effect of Sitosterol On the Hyperlipemia of Myxedema

Maurice M. Best, Charles H. Duncan and Joan D. Wathen. From the University of Louisville School of Medicine, Louisville, Ky.

Myxedema is commonly accompanied by an increase in the serum levels of cholesterol and othe

lipids. Sitosterol, which has been shown to effect a reduction in serum lipids of euthyroid subjects, has been administered to a group of patients with myxedema. Included were cases of post-thyroidectomy, I^{131} induced and spontaneous myxedema. Sitosterol was administered before eating in daily dosage of 20 to 25 Gm.; there was no restriction on the type or amount of food. Fasting serum lipids were determined at 1 to 3-week intervals during control and sitosterol periods.

A reduction of all serum lipids resulted from the administration of sitosterol. Total cholesterol was reduced from a mean level of 357 mg. per 100 ml. (range 241 to 605) to 275 mg. per 100 ml. (range 175 to 419). In terms of per cent of control level, the mean fall in cholesterol was 21.6 per cent (range 13.3 to 31.9 per cent). The mean control and sitosterol treatment levels of the other serum lipids were as follows (in mg. per 100 ml.): lipid phosphorus 15.9 and 12.8, neutral fat 373 and 292, and total lipid 1128 and 886. These results are similar to those previously reported from this laboratory for euthyroid patients. The mechanism of action of sitosterol and the relation of dietary cholesterol to sitosterol effect in myxedema, as demonstrated by animal experiments, will be discussed.

10:40

6. The Effect of Beta and Dihydro-Beta-Sitosterol on the Serum Lipids of Patients With Coronary Atherosclerosis

Alfred Steiner and Fletcher P. Riley. From the Research Service, First (Columbia), Goldwater Memorial Hospital, and the Department of Medicine, College of Physicians and Surgeons, Columbia University, New York, N. Y.

Recent studies by Duncan and Best, and Joyner have shown that the oral administration of sitosterol to human subjects resulted in significant lowering of the serum cholesterol level. Parallel studies have been made to determine the effect of plant sterols on the serum lipid values of patients with coronary artery disease. Beta and Dihydro-β-Sitosterol (Cytellin, Lilly) in oral doses of from 19 to 53 Gm. per day were given to 6 hospitalized and 4 ambulatory patients for periods of from 2 to 5 months. The serum lipid values were determined during the feeding of the sitosterol and a comparable placebo preparation administered in alternating periods. The diet of the hospitalized patients remained constant during the periods of observation.

The results of sitosterol administration are not as striking as those which have been previously reported. However in six patients, falls in serum cholesterol of from 10 to 14 per cent occurred during the feeding of sitosterol as compared to initial control or placebo periods. A decrease in the variability of the serum cholesterol level of 4 of 6 hospitalized patients was apparent during the feeding of plant sterol.

11:00

7. Analysis of Some Variables in Studies With Serum Cholesterol-Lowering Agents

Arthur H. Levere, Richard C. Bozian, R. S. Jackson and Chas. F. Wilkinson, Jr. From the Department of Medicine, New York University Post-Graduate Medical School, New York, N. Y.

The inconsistent results which have been reported with the use of serum cholesterol-lowering agents, such as vegetable sterols, prompted an analysis of experimental conditions for uncontrolled variables. A number of such factors were identified.

In human studies, the apparently unequivocal successes with the "sitosterols" have been with patients who were "hypercholesterolemic." The "hypercholesterolemic state," however, is not a distinct entity, but a mixed group with varying manifestations and characteristics governed by a number of hereditary and acquired factors. Spontaneous fluctuations of serum cholesterol in man have been found to exceed the usually accepted limits, particularly in the older age group and among certain subjects with hypercholesterolemia; therefore, an accurate definition of the variety of hypercholesterolemia being treated would seem necessary. Infrared spectrophotometric and melting point studies are presented which demonstrate that all "sitosterol" preparations are not identical.

11:20

8. Further Observations On The Metabolism of Cholesterol in the Dog

E. H. Mosbach, L. L. Abell, and F. E. Kendall. From the Columbia University Research Division, Goldwater Memorial Hospital and the Departments of Biochemistry and Medicine, Columbia University, New York, N. Y.

The excretion of cholesterol and bile acids was determined in euthyroid and hypothyroid dogs on low and high cholesterol intakes in order to find out whether the thyroid state or the level of cholesterol intake affect the conversion of cholesterol to bile acids. The small dogs (2.1 to 4.8 Kg.) used in this study ingested on the average 22 mg. of cholesterol per day when placed on the standard low cholesterol diet. On this regimen the animals excreted 79 mg. of cholesterol (but no coprosterol) and 85 mg. of bile acid daily. When thiouracil (200 mg. per day) was given the same animals, no significant changes in the cholesterol and bile acid excretion were observed, although this dosage of thiouracil was sufficient to lower the BMR and to raise the serum cholesterol level. After a suitable control period, the animals

were fed a high cholesterol diet; on the average they ingested 1.46 Gm. of cholesterol daily. The dogs responded to the high cholesterol intake by excreting 1.14 Gm. of cholesterol and 430 mg. of bile acid per day. Thus, all of the ingested cholesterol could be accounted for as fecal cholesterol plus bile acid. On the high cholesterol diet plus 200 mg. of thiouracil per day the average cholesterol intake of the dogs was 1.68 Gm. per day. On this atherosclerosis-producing regimen the dogs excreted 1.31 Gm. of cholesterol daily. Their bile acid excretion fell to 195 mg. per day.

These results indicate that thiouracil did not alter the sterol or bile acid excretion of dogs on the low cholesterol diet. On high cholesterol intakes, thiouracil appeared to reduce the capacity of the animals to convert cholesterol to bile acids.

11:40

9. Morphologic and Histochemical Studies on the Development and Progression of Arteriosclerosis

Henry Z. Movat and Robert H. More. From the Department of Pathology, Queen's University, Kingston, Ontario, Canada.

The present study is an inquiry into some of the local mechanisms which may play some role in the development of the arteriosclerotic lesions. Current autopsied cases, taken at random, form the basis of this study. Lesions which appeared grossly as fatty flecks or streaks, as small, transparent white or yellow plaques, as larger similar plaques and as diffusely transparent (gelatinous) areas were examined.

The small transparent plaques or diffusely gelatinous appearing areas seemed to represent early lesions. What was considered the earliest lesion consisted of edema, precipitation of fibrin causing diminution or complete disappearance of Alcian blue positivity and separation of connective tissue elements. Some gelatinous plaques were frequently made up of abundant Alcian blue positive ground substance. This lesion was interpreted as a further development of the edematous plaque. Finely dispersed lipid could be demonstrated in both types of lesions. In the earliest lesions when there was extreme accumulation of fluid with formation of plasma pools, these always contained abundant very finely dispersed lipid. Intracellular lipid was more abundant in the later lesion. The fatty streaks and flecks consisted usually of foam cells, extracellular lipid, acid mucopolysaccharide rich tissue and sclerotic, i.e. collagenous tissue. White plaques were made up to varying degrees of acid mucopolysaccharides, collagenous tissue, fibrinoid, hyaline and varying amounts of lipid.

Morphologic and histochemical studies also were carried out on the fibrinoid occurring in arteriosclerosis. It was found that although fibrin may be deposited on the surface of the aorta and later incorporated into the wall (Duguid, 1946–1952), more frequently this "fibrinoid" is formed by "insudation" and precipitation of fibrinogen into the loosened intima followed by conglomeration. This material is PTA and PAS positive and is an acidophilic (basic) protein in which the following amino acids have been identified histochemically: tyrosine, tryptophane, histidine, cysteine and cystine.

It was concluded from these studies that some of the earliest changes in arteriosclerosis probably represent a lipoprotein containing edema which develops first into a mucinous and later into a hyaline-collagenous plaque. Lipids seem to be present first in a diffuse, dispersed form. They become visible first as small and later as larger droplets, as the lesions are gradually depleted of fluid. It is believed that the proteins in the edema furnish the matrix (nutrient) for the formation of mucinous tissue just as the "feed" does in tissue cultures (Grossfeld et al., 1955). The mucinous tissue in turn serves as matrix to the formation of sclerotic tissue. The mucinous tissue contains abundant acid mucopolysaccharides while the scar tissue is in addition rich in mucoproteins.

12:00

Luncheon, Guest Lecturer: W. C. Hueper

The Relationship between Arteriosclerosis and Cancer

2:00

Business Session

2:20

Presidential Address. Louis N. Katz

SUNDAY AFTERNOON

Arthur C. Corcoran, Presiding

2:40

10. Structure of the Great Vessels as Seen with the Electron Microscope

Henry C. McGill, Jr., Jack C. Geer, Frank N. Low and Russell L. Holman. From the Departments of Pathology and Anatomy, Louisiana State University School of Medicine, and the Electron Microscope Laboratory at Charity Hospital of Louisiana at New Orleans, La.

Ultrathin sections of the aorta and pulmonary artery taken from dogs and humans have been examined under the electron microscope. These tissues show a remarkably complex structure, com

posed of endothelium, unit fibers of collagen, elastic fibers of all sizes, smooth muscle, "tissue space" presumably filled with mucopolysaccharide and spherical structures up to 2 μ in diameter which have not yet been identified. These unidentified bodies correspond to spaces seen in the light microscope sections which were previously thought to represent fixation artefacts, but under the electron microscope, they possess a definite structure. The human aorta has a structure substantially similar to that of the dog, but is more difficult to interpret because of autolytic changes.

The proportions and relationships of the various structures which make up the vessel wall vary greatly at different levels within the wall. A remarkable feature is the relatively high proportion of "tissue space" between the cells and visible, formed elements, particularly, just beneath the endothelium and in the inner third of the media. The complex organization of many elements into a definite pattern indicates that these vessels should be considered as highly specialized organs having more than a simply supportive function.

3:00

11. The Effect of Triton WR-1339 on the Activity of Cholesterol Esterases

W. James Kuhl, Jr. From the Department of Medicine, College of Medicine, New York University-Bellevue Medical Center, New York, N. Y.

Triton WR-1339, it has been reported, will produce hypercholesteremia, hyperlipemia and hypercholatemia in animals, and an acceleration of hepatic synthesis of cholesterol from labelled acetate in both the normal and cholesterol-fed rat, with an increased equilibration of cholesterol between serum and liver. Since these changes might reflect different enzymatic handling of cholesterol, the effect of Triton in vitro on cholesterol esterases was studied and compared to the known effects of cholate.

The activity of partially purified beef pancreas, rat liver, and human plasma cholesterol esterases was determined after incubation with cholate and Triton. As is known, cholate, at levels of 1 to 4 per cent, induces markedly increased hydrolysis of cholesterol esters by pancreatic esterase, increases hydrolysis of esters by liver esterase, and arrests esterification by plasma esterase. No effect of cholate was noted when used in concentration of 0 to 20 mg. per cent. Triton at concentrations of 0 to 1200 mg. per cent in the presence of 0 to 20 mg. per cent added cholate did not induce hydrolysis by pancreatic or liver esterase. However, Triton at a concentration of 300 mg. per cent produced partial inhibition of esterification by human plasma esterase and almost complete inhibition at 600 to 1200 mg. per cent. This effect of Triton was slightly enhanced by the addition of 10 or 20 mg. per cent of cholate when the inhibition was partial, but no effect of added cholate was noted at the higher levels of Triton.

Since both cholate and Triton will produce an inhibition of the esterifying activity of plasma cholesterol esterase, it is suggested that this altered enzyme activity plays a role in the production of the hypercholesteremia.

3:20

12. Alkaline Phosphatase Activity in Early Atherosclerotic Plaques

J. C. Paterson, T. Moffatt and Jean Mills. From Westminster Hospital, Department of Veterans' Affairs and the Collip Medical Research Laboratory, University of Western Ontario, London, Ontario, Canada.

In a presentation read by title to this society last year, we reported on the ease with which deposits of hemosiderin can be demonstrated in human atherosclerotic plaques by the use of gross staining methods (Prussian blue). Extraordinary amounts of hemosiderin have been demonstrated thus, not only in advanced lesions but also many times in pearly plaques and occasionally in fatty streaks, that is, in the earliest recognizable manifestations of the human disease. Since hemosiderin deposition appears to be a constant feature of the atherosclerotic process, an elucidation of its origin becomes a matter of some urgency. One explanation, and to us the most plausible, is that the iron results from the leakage of blood from pre-existent intimal capillaries. This implies that there is a capillary blood supply to the earliest lesions of atherosclerosis, something we have been unable to demonstrate by ordinary staining methods. However, when the alkaline phosphatase method, as modified by Gomori, is employed on serial sections, activity is observed in structures which we interpret as capillaries. Activity of this kind has been demonstrated so far in each of 6 fatty streaks or flecks, in each of 5 tiny pearly plaques, and in 2 out of 3 specimens in which no atherosclerotic lesions were visible. Photomicrographs of these structures will be shown and the general picture of hemosiderin deposition in atherosclerotic plaques will be reviewed.

3:40

13. An Enzymatic Defect Associated with Altered Lipoprotein Metabolism in an Individual with Idiopathic Hyperlipemia

Richard J. Havel and Robert S. Gordon, Jr. From the Laboratory of Metabolism, National Heart Institute, Bethesda, Md.

Studies of certain aspects of lipid transport in a patient with idiopathic hyperlipemia have provided data concerning the mechanism of his hyperlipemic

state. The excess lipid was present entirely in particles having the flotation and chemical characteristics of chylomicra. The S_f 0–10 and high density lipoprotein concentrations were markedly reduced. The serum triglyceride concentration varied directly with the fat content of isocaloric diets. On a fat-free diet the serum triglyceride and low density ($S_f > 10$) lipoprotein concentrations fell markedly, the former to within normal limits. The S_f 0–10 lipoprotein concentration increased and the chemical composition of all fractions became normal. At a time when the fasting serum triglyceride concentration was normal, the rate of removal of ingested fat from the blood was greatly reduced, lipemia persisting for 24 to 48 hours. Caloric restriction and repletion while the patient was on the fat-free diet failed to produce significant alterations in serum lipid and lipoprotein concentrations, although the fasting R.Q. was reduced to 0.73. This suggests that endogenous lipid transport was unimpaired and therefore carried on by a mechanism differing from that of exogenous lipid transport. In the patient as well as in two hyperlipemic siblings, lipoprotein lipase (lipemia clearing factor) activity, as measured by optical clearing in vitro, could not be demonstrated after anticoagulant doses of intravenous heparin, although small amounts were present as measured by in vitro production of unesterified fatty acids. Acute and intensive chronic heparin administration failed to significantly reduce the patient's abnormal lipoprotein and triglyceride concentrations. It is suggested that the observed defect in plasma lipoprotein lipase activity accounts for the slow rate of removal of ingested fat from the blood in this patient and the resultant persistent chylomicronemia.

4:00

14. The Beta-2 Lipoproteins of Human Serum

Henry G. Kunkel and Rodes Trautman. From the Rockefeller Institute for Medical Research, New York, N. Y.

Phospholipid and cholesterol determinations were carried out on lipid extracts of segments obtained by zone electrophoresis of serum in various supporting media in which adsorption does not interfere. The α_1 and β_1 lipoproteins do not account for all the lipid material, there being some of intermediate mobility ("α_2 region"). This ranged between 4 and 38 per cent of the total phospholipid in a limited group of normal and atherosclerotic individuals. The quantity of lipid in this region was relatively constant in repeat experiments but some shifts in the shape and mobility distribution of this heterogeneous fraction were encountered.

A number of sera were separated at their own protein-free density into a top and bottom fraction using ultracentrifugal flotation in the swinging bucket rotor. Electrophoresis of the bottom fraction indicated that the phospholipid and cholesterol in the α_2 region was greatly diminished, while that in the α_1 and β_1 regions was not significantly reduced. The isolated top fraction was also studied by zone electrophoresis, an experiment that is not feasible in moving boundary electrophoresis because of gravitational instability. When special precautions were taken to avoid autoxidation, and albumin was added to bind fatty acids, this top material had a mobility in the α_2 region, and accounted for the difference between the bottom fraction and the whole serum. A correlation was thus suggested between at least part of the electrophoretic α_2 fraction, which also contains chylomicrons, and the class of lipoproteins less dense than $d^{2}_{4}{}^{0}$ 1.007 (Gofman $S_f > 17$). In addition to these very light lipoproteins, some high density lipoproteins were found in several sera in this α_2 region.

4:20

15. Beta-2 Lipoproteins in Myocardial Infarction

Emery C. Miller, Jr. From the Bowman Gray School of Medicine, Wake Forest College, Winston-Salem, N. C.

An inexpensive, accurate method of serum lipoprotein determination by paper electrophoresis is reported. The intensity of protein and lipid staining of simultaneously-run serum samples is read directly. The height of that section of the lipid curve bounded by a 1 cm. area that most nearly approximates the latter half of the beta globulin of the protein curve is measured in mm. The fraction measured corresponds in a general way to the S_f 10–20 fraction of Gofman and the −S 40–70 group of Page, and is increased in sera in which the cholesterol to phospholipid ratio is altered in the direction of unity or greater. In sera with such marked increases in chylomicrons as to appear lipemic to the eye the determination is unreliable. A large adsorption peak appears at the baseline. This pattern, however, is in itself abnormal.

Total serum cholesterol was above 225 mg. per cent in 52 per cent of 27 patients with appropriate clinical picture and classical ECG changes of myocardial infarction. Ninety-three per cent had abnormal beta-2 lipoprotein values. The average is 34, with a range of 25 to 51 mm. In 104 student nurses the average is 15 mm., the range 8 to 23. 0.25 mg. stilbesterol p.o. per day caused a slow, progressive fall toward normal in 11 of 12 patients without significant side-effects in males.

The method of lipoprotein determination described is inexpensive, technically simple and reproducible. It appears to possess considerable accuracy in indicating abnormal lipid metabolism in patients having coronary atherosclerosis clinically. This

method may be more adaptable to routine clinical use than the determination of cholesterol to phospholipid ratios or ultracentrifugal classes of serum lipoproteins.

4:40

16. The Conjugated Lipids of Serum and Aortic Intima of the Rabbit, Dog and Human. (Lipids and Amino Acids of the Cohn Fractions)

Robert J. Boucek, Nancy L. Noble and Kung Y. T. Kao. From the University of Miami Medical School, Miami, Fla.

Conjugated lipids obtained from the serum and from the saline-soluble and -insoluble fractions of the aortic intima were quantitatively analyzed for the following constituents: total protein, total and choline-containing phospholipid, total and esterified cholesterol, neutral fat, total lipid and 19 amino acids. A difference in the distribution of the protein between the serum and tissue was noted in all the species. The protein of the serum was equally divided between the α and the β fractions in the dog, whereas in the human there was a greater proportion in the α fraction. The protein of the β fraction of the serum of the female rabbit was lower than any of the studied species. In the intima of the three species, most of the protein was found in the saline-insoluble residue. Little protein was found in the tissue α fraction. The proportion between α and β protein was 2 to 1 or 1 to 1 in the serum, but in the intima, the proportion was 1 to 5 or 1 to 6.

The cholesterol of the serum was equally divided between the α and β fractions in the rabbit and dog, while in the human, most of the cholesterol was located in the β fraction. The phospholipids were found chiefly in the α fraction. In the intima, the greatest concentration of the lipids was found in the saline-insoluble residue fraction. This fraction has been identified by its amino acid concentrations to be elastin and collagen. When the concentration of protein was highest in the residue fraction, the concentration of cholesterol was likewise elevated. No similar relationship existed between the concentrations of phospholipids and protein.

The majority of sex and species differences in the concentration of amino acids was found in the saline-soluble α-β fraction of the tissue. This fraction appeared to be the ground substance of connective tissue. The human intima was richer in lysine, cystine and tryptophane than the intima of the dog or the rabbit. The amino acid composition of the residue fractions was similar in most respects in all species and sexes. The amino acids were divided equally between α-β fractions of the serum and resembled the concentration of the α and β fractions of the tissue in all species.

5:00

17. Plasma, Plasma Lipoproteins and Chylomicrons in Vascular and Avascular Connective Tissue

L. L. Waters. From the Department of Pathology, Yale University School of Medicine, New Haven, Conn.

In an effort to gain an understanding of some of the basic etiologic and morphologic phenomena occurring in the development of the arteriosclerotic lesion, reactions to injected plasma, plasma lipoproteins and chylomicrons have been studied in various tissue sites. Injected subcutaneously into dogs, human plasma or precipitated, undenatured human plasma lipoproteins are rapidly removed without lesion formation. Injected directly into the wall of the dog's carotid artery or aorta, these substances are completely removed without formation of a lesion other than that of the trauma involved. Placed subcutaneously in dogs, dog or human, chylomicrons persist longer than soluble plasma-lipid fractions, but are generally removed without significant lesion. Dog or human chylomicrons injected directly into the dog's aorta wall are incorporated within a week to 10 days into a foam-cellular lesion, simulating an inflammatory xanthoma. Injection of dog or human chylomicrons into the corneas of dogs results in a foam-cellular lesion with strikingly reduced inflammatory components. The introduction of chylomicron-free human plasma, serum or lipoprotein into the dog's cornea leads to variations of this fatty lesion. From a sequential study of these experimental changes, it has been possible to learn something about the lesion-producing potentiality of important classes of plasma substances in connective tissue, about the timing and sequence of events that occur and about the modifying role of the particular connective tissue environment.

6:30

Cocktails

MONDAY MORNING
NOVEMBER 6, 1955

E. C. Andrus, Presiding

8: 30

Registration

9 : 00

18. Insulin Inhibition of Diet-Induced Regression of Coronary Atherosclerosis in Chicks

J. Stamler, R. Pick and L. N. Katz. From the Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago, Ill.

Cholesterol-induced hyperlipemia and atherosclerosis in chicks rapidly regress upon cessation of

cholesterol feeding and re-institution of a plain mash diet. The present experiment was undertaken to assess the effects of insulin on this regression process. In two series of experiments, chicks were fed a mash supplemented with 2 per cent cholesterol and 5 per cent cottonseed oil (2 CO). After five weeks on this regimen, one-third of the birds were sacrificed. The other two-thirds were divided into two groups, both fed an unsupplemented plain mash diet. One group also received a daily injection of a long-acting insulin (20 units). After two weeks, both groups exhibited practically complete disappearance of the previously existing hypercholesterolemia, with beginning regression of aorta lesions. The control group, receiving no hormone, exhibited significant regression of coronary lesions. In contrast, regression of coronary lesions was absent in the insulin-treated group, despite restoration of plasma lipids to normal levels. These findings pose fundamental problems concerning the relationship of exogenous insulin to atherogenesis in diabetic patients.

9:20

19. Suppression of Estrogen Anti-Atherogenesis by Hypothyroidism in Cholesterol Fed Chicks

R. Pick, J. Stamler and L. N. Katz. From the Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago, Ill.

In an effort to gain insight into the mechanisms of estrogen inhibition of coronary atherogenesis in cholesterol fed chicks, a series of experiments has been in progress combining estrogens with other hormones. It was previously shown that androgen administration, pancreatectomy or hydrocortisone-induced hyperadrenocorticism with corticoid diabetes all failed to alter estrogen-induced plasma lipid patterns and anti-atherogenesis.

In the present experiment, an assessment was made of the effects of thiouracil-induced hypothyroidism on estrogen anti-atherogenesis. Two series of chicks were utilized, each consisting of 40 birds divided equally into four experimental groups. In the first series cockerels were studied, in the second young, sexually immature pullets, known not to differ from young males in their atherogenic response. All four groups ate a diet supplemented with 2 per cent cholesterol and 5 per cent cottonseed oil; the groups were: 1, control; 2, estrogen treated; 3, thiouracil fed; and 4, thiouracil plus estrogen treated. The results in the two series were essentially identical. After five weeks on the experimental regimen, the incidence of coronary atherogenesis was: group 1, 92 per cent; 2, 7 per cent; 3, 100 per cent; and 4, 63 per cent. The group 4 thiouracil-treated chicks, exhibiting partial reversal of estrogen-induced anti-atherogenesis, maintained the typical estrogen-induced blood lipid pattern. It is concluded that (1) thiouracil-induced hypothyroidism is the first procedure demonstrated to be capable of overcoming estrogen prophylaxis of coronary atherogenesis and (2) a euthyroid state, apparently, is a prerequisite for the protective action of estrogens on the coronary arteries of cholesterol-fed chicks.

9:40

20. Factors Influencing the Biosynthesis of Lipids by Calf Aorta In Vitro

N. T. Werthessen, Melvin Nyman, Jack P. Strong and Russell L. Holman. From the Department of Pathology, Louisiana State University School of Medicine, New Orleans, La.

Continuing studies on the metabolism of lipids, utilizing the excised calf's aorta in vitro have shown that the biosynthesis of cholesterol and fatty acids by the aorta can be influenced by a number of factors. The technic of perfusion, previously described, has been employed throughout. The use of nitrogen and carbon dioxide atmospheres in the system has shown that the biosynthesis of lipids by the organ is reduced by the absence of oxygen. Through the use of several hormones and through the combined perfusion of several glands and organs, observations have been made on the capacity of these organs to influence the metabolism of lipids in the aorta.

By the use of artificial media and the admixture of various proportions of serum, it has been possible to demonstrate the presence of a substance or system in serum which seems to inhibit the biosynthesis of cholesterol by the aorta as measured by isotope incorporation.

Sudan stains of frozen sections of the perfused aortas have confirmed the chemical findings but have indicated a lag period of 24 to 48 hours in the appearance of stainable lipid. This lag period may indicate that processes other than cholesterol and fatty acid synthesis are involved in the appearance of the stainable lipid. Control observations have excluded autolytic processes. Regardless of the interpretation, the use of aortas, perfused under standard conditions in vitro for 72 hour periods, offers a bioassay technic for the study of agents influencing lipid deposition; results obtained by this technic will be presented.

10:00

21. An In Vitro Study of Atherogenesis in Rabbits

Silas M. Evans, David Mountain, Kenneth D. Brown, Harry K. Ihrig, Walter Zeit and Eugene R. Haushalter. From the Marquette University School of Medicine, Milwaukee, Wis.

In previous years, we have reported the results of pulsating human bloods against normal human aortas and demonstrated a significant correlation

between results so obtained and the source of the blood used. It has been found that the data so obtained presented an artifact caused by the use of sodium oxalate as an anticoagulant, as well as significant lipid deposits. This, to a degree, invalidates some of our earlier results.

The present report presents data obtained by pulsating rabbit sera without anticoagulant against fresh normal rabbit aortas under standardized conditions. A deposition in the intima of birefringent, sudanophilic digitonin precipitable material was consistently demonstrable when sera was obtained from rabbits with chronic dietary hyperlipemia and hypercholesterolemia. Sera from normal control rabbits failed to show this. These in vitro deposits closely resembled the atheroma in the aorta of the hypercholesterolemic rabbits, and possessed the same birefringence, staining characteristics and solubility properties.

It is also shown that the β fraction of lipoproteins separated from pools of test hypercholesterolemic sera and extended to volume with normal saline solution possessed the "positivity" properties, whereas the α fraction did not. The effects of variations in time and pressure upon the quantity and quality of the described depositions are demonstrated.

10:20

22. In Vitro Studies on Human Hepatic Cholesterol Synthesis

C. Bruce Taylor, G. E. Cox, L. G. Nelson, C. B. Davis, Jr. and G. M. Hass. From the Rush Departments of Pathology & Surgery, Presbyterian Hospital, Chicago, Ill.

In vivo studies in the human have failed to provide quantitative estimations of cholesterol synthesis by specific tissues. This is due to the rapid interchange of newly synthesized cholesterol between various tissues and to the difficulty of obtaining tissue biopsies at appropriate times. Since postmortem hepatic tissues showed a marked loss of cholesterol synthesis when conventional incubation technics were employed, surgical hepatic and intestinal biopsies were obtained during operative procedures for other purposes. Tissue slices were incubated for three hours with radioacetate. Cholesterol synthetic rates were calculated as mg. of cholesterol per 100 Gm. of tissue per hour. Each patient's dietary history was evaluated and cholesterol concentrations of serum, liver and intestinal tissue were determined. In middle-aged patients hepatic cholesterol synthesis from radioacetate averaged from 0.1 to 0.3 mg. per 100 Gm. liver per hour. Intestinal cholesterol synthesis approximated that of liver. There was no apparent correlation between hepatic cholesterol synthesis and relative quantities of cholesterol and fat habitually ingested by the patient. Short term feeding of large doses of cholesterol with cream resulted in synthetic rates only slightly lower than those of patients on a conventional American diet. Since earlier studies in experimental animals have shown marked suppression of hepatic cholesterol synthesis by dietary cholesterol, the present studies suggest that in humans on conventional diets, containing small to large quantities of cholesterol, hepatic cholesterol synthesis is also suppressed. At this time maximal human hepatic cholesterol synthesis is not known; its determination may require data from patients on cholesterol-free diets for prolonged periods.

10:40

23. Lipfanogen and Antilipfanogen Determinations on Serum Lipoprotein Fractions

Henry S. Simms, Frank T. Lindgren and Charles R. Harmison. From the Department of Pathology, Columbia University, College of Physicians and Surgeons, New York, N. Y. and the Division of Medical Physics, University of California, Berkeley, Calif.

Fasting human serum has been separated into lipoprotein fractions by means of the preparative ultracentrifuge. These fractions have then been tested for their content of lipfanogens and antilipfanogen. Although toxicity interfered with some of the tests, the following results were obtained:

The lipoprotein fractions S_f 0–20, S_f 20–400, as well as the total high density lipoprotein fraction, were found to contain very little of the lipfanogens (either free or total), or of antilipfanogen (free or total), or of the complex (between the two) and also little of the precursors.

On the other hand, the major portion of these agents from each sample of serum was found to be in the ultracentrifugal lipoprotein "residue" fraction from which nearly all the lipoproteins known to be present in the serum had been removed. The antilipfanogen was proportionally somewhat high in this residue fraction. These results indicate that the lipfanogens are not identical with any of the major lipoprotein fractions.

11:00

24. Response of Serum Lipids and Urinary Ketosteroid Excretion Patterns to Estrogen Therapy in Coronary Atherosclerosis

R. W. Robinson, W. D. Cohen and N. Higano. From the Memorial Hospital, Worcester, Mass.

In the light of the pronounced estrogen effects on the course of experimentally induced atherosclerosis in animals and the recent interest in estrogen therapy of human atherosclerosis, this project was undertaken to examine the physiologic effects of estrogens on the serum lipid patterns and urinary steroid excretion in patients with myocardial infarction.

Two groups were studied, (1) middle-aged males with myocardial infarction on (a) oral mixed conjugated equine estrogens (Premarin) and low-fat diet, (b) Premarin and free diet, (c) placebo and low-fat diet, (d) placebo and free diet, (e) oral stilbesterol for two to three years and (2) Two groups of normals were also studied (a) middle-aged males and (b) ovulating females, at intervals in the menstrual cycle.

After routine clinical evaluation the following serum lipid determinations were performed; cholesterol, phospholipid, and cholesterol content of the "α"- and "β"-lipoproteins as separated by paper electrophoresis. In addition, urinary ketosteroids were fractionated by gradient elution chromatography on alumina after hydrolysis of conjugates by β-glucuronidase plus acid. These studies were then repeated 1, 3, 6 and 12 months after initiation of estrogen therapy.

Statistical analysis of the serum lipid data revealed a significant lowering of cholesterol after 6 months, and a significant increase of phospholipid after 3 months of therapy. The mean cholesterol to phospholipid ratio showed a progressive decrease during twelve months. The ratio of β- to α-lipoprotein cholesterol showed a highly significant decrease after one month, which was maintained thereafter. Urinary ketosteroid excretion studies have shown that the mean daily total 17-ketosteroids were lowered during treatment. Therapy also resulted in a striking increase of urinary dehydroepiandrosterone excretion, moderate decrease in androsterone and etiocholanolone, and little change in total 11-oxygenated-17-ketosteroids (sum of 11-ketoetiocholanolone, 11-hydroxyandrosterone and 11-hydroxyetiocholanolone). The significance of the serum lipid and urinary ketosteroid data will be discussed.

11:20

25. The Clinical and Pathologic Significance of Atheromatous Embolization with Emphasis on an Etiology of Renal Hypertension

Fred P. Handler. From the Departments of Pathology, Jewish Hospital and Washington University School of Medicine, St. Louis, Mo.

The discharge from eroded atheromatous plaques of cholesterol crystals, hyaline and occasional bits of calcified debris results in a peculiar but typical alteration in affected arteries.

Cholesterol crystal emboli arising from eroded atheromatous plaques have up to now been reported in 13 patients since 1945; the present report deals with 7 additional cases bringing the total to 20. The course of arterial changes is probably spasm, granulomatous endarteritis, intimal fibrosis with sequestration of the cholesterol crystals and marked diminution of lumen diameter. Tissues distal to the progressive fibrosing endarteritis become ischemic, resulting in impaired function and nutrition, atrophy and sometimes necrosis. Ischemia and atrophy of renal cortex is diffuse and marked if vascular lesions are plentiful. Associated clinical data suggest the activation of the renal hypertensive humoral mechanisms as manifested by an abrupt rise in blood pressure and in intensification of existing hypertension noted in three patients of this series.

11:40

26. Presence and Role of Mast Cells in the Arterial Wall in Man

O. J. Pollak, Dover, Del.

It has been postulated that serum lipoproteins entering the arterial wall are broken up by heparin of tissue mast cells. Preliminary post mortem studies of the aorta and some branches were made. The number of basophiles in normal human arteries is small. They are confined to the intima and subintima. Their number at various locations in the arterial network has not yet been ascertained. Age and sex differences have not yet been studied.

In arteries of patients who died in shock, mast cells are numerous. Their number is also high in early atheromatous patches while they are absent in advanced (pearly) plaques. Many of the mast cells are located between intimal endothelium cells. This suggests hematogenous origin of these cells as does their presence in the adventitia in shock. The location of mast cells in the intima and subintima corresponds to the common site of lipophages in atherogenesis. Superficially located mast cells are round and contain many large basophilic granules. Deeper-seated mast cells are oval to polyhedric and have fewer and smaller granules. Instead, they contain large vacuoles. Possible metamorphosis of mast cells into lipophages is suggested. These observations strongly support the concept that atherogenesis is initiated by alterations ascribed to shock (Circulation **5:** 539, 1952). Multiple new avenues of research are being opened.

12:00

Luncheon

MONDAY AFTERNOON

Chas. F. Wilkinson, Jr., Presiding

2:00

27. The Aggravating Effect of Cholesterol on Cardiovascular Disease Induced by Choline Deficiency

George F. Wilgram, Charles H. Best and Lena A. Lewis. From the Banting and Best Department of Medical Research, University of Toronto, Toronto Canada and the Cleveland Clinic, Cleveland, O.

Severe choline deficiency is one of the numerous procedures which produce arterial disease in experi-

mental animals. The lesions consist of fatty infiltration of cardiac muscle fibers with subsequent necrosis, and of lipomatous infiltration of coronary arteries and of the aorta.

In the coronary arteries, this fatty infiltration is followed by endothelial hyperplasia with occasional plaque formation and medial thickening. In the aorta the endothelial fat infiltration is followed by medial degeneration and necrosis with subsequent calcification and fibrosis of the involved areas. There is, however, no true atheroma formation as the reactivity of the vascular tissue of the rat to the infiltrated lipid is apparently different from that of the human and some other animal species.

The aorta of the rat has no medial vasa vasorum and this may account for the fact that our lesions exhibit no foam cell formation and no vascular proliferation to the infiltrated lipid (Hartroft). PAS positive staining material, however, is augmented in older lesions in coronary arteries and aortas.

Our basal choline-deficient diets are cholesterol free. However, when cholesterol is added at a 2 per cent level to these diets, the severity and incidence of cardiovascular lesions are greatly increased. Choline supplements prevent the ill effect of choline deficiency and also the aggravating effect of cholesterol. No lesions are apparent in choline-supplemented animals.

The blood cholesterol levels are decreased in cholesterol supplemented choline-deficient animals as compared with choline-supplemented controls. The low-density lipoproteins are decreased but the β classes of lipoproteins are about the same in choline-deficient as in choline-supplemented rats when 2 per cent cholesterol is added to the diet.

It has not yet been determined whether this aggravating effect of cholesterol on choline-deficient tissues is due to a direct atherogenic action on the vessel walls or to an increase in the damage to the choline-deficient kidney; the significance of this effect in the production of cardiovascular disease in choline deficiency has not yet been settled. These experiments show that cholesterol has a very potent aggravating effect on the induction of cardiovascular disease in choline-deficient rats, although there is no hypercholesterolemia, hyperlipemia or beta hyperlipoproteinemia.

2:20

28. Persistent Hyperlipemia Following Injection of a Clearing Factor Inhibitor (CFI) Obtained from Plasma

Joseph Seifter and David H. Baeder. From the Wyeth Institute for Medical Research, Philadelphia, Pa.

CFI described by us (Seifter, J. and Baeder, D. H.: Proc. Soc. Exper. Biol. & Med. **86:** 709, 1954) was separated from plasma, freeze-dried and prepared pyrogen-free and sterile for injection. In fasted mice, rats, rabbits, guinea pigs and dogs, 1 mg. per Kg., intravenously, produced hyperlipemia in the 468 animals injected. Hyperlipemia also appeared in rats administered 5 mg. per Kg. intramuscularly. No toxic manifestations were seen after intramuscular injection of 100 mg. per Kg. and the hyperlipemia which was associated with an engorgement of thoracic lymph ducts and dark brown perirenal and intercostal fat persisted at least five days. Intravenously the LD_{50} was in the range of 50 to 60 mg. per Kg., the deaths apparently resulting from flocculation shock.

CFI prevented decrease of optical density by heparin, hyaluronidase and hyaluronate released clearing factors whereas diisopropyl fluorophosphate (DFP), sodium cholate and protamine prevented only the action of heparin clearing factor. Sodium cholate (10 mg. per Kg. intravenously) did not produce hyperlipemia in rats or in dogs. Intravenously DFP in doses of 5 and 50 μg. per Kg. also failed to produce hyperlipemia in dogs. CFI or protamine induced hyperlipemia resulted in approximately a two-fold increase in plasma levels of cholesterol, lipid phosphorus and fatty acid.

2:40

29. Hereditary Obesity: Relation to Serum Lipoproteins and Protein Concentrations in Swine

L. A. Lewis and I. H. Page. From the Research Division of the Cleveland Clinic Foundation and the Frank E. Bunts Educational Institute, Cleveland, O.

In mice, the obesity-hyperglycemia syndrome is associated with hypercholesterolemia. However, association of hypercholesterolemia with hereditary obesity in other species is not well documented. The present studies were aimed at defining this association in miniature swine, using contrasting strains, the one long and lean and the other short and fat.

The pigs were fed a diet of ground oats, corn and SMA formula with multivitamin and extra vitamin D. Blood was sampled every two weeks from about three months of age. Serum lipoproteins were determined ultracentrifugally by the method of Lewis, Green and Page, serum proteins by moving boundary electrophoresis and cholesterol by the method of Abell and Kendall.

The long-lean pigs gained an average of 0.9 Kg. weekly in body weight during the first 20 weeks, while the short-fat animals averaged 1.7 Kg. At this point, Aureomycin was added to the ration (10 mg. per 10 lb.) and, in the next 10 weeks, respective weight gains were 2.2 and 2.1 Kg. weekly. Serum cholesterol of the lean pigs averaged 136 mg. per 100 ml. while that of the fat pigs averaged 184. The fat pigs, correspondingly, had higher serum lipoprotein concentrations in the range −S 20–40 and lower

densities, although they showed little difference in the high density −S 1–10 fraction.

A higher serum albumin concentration accounted for most of the higher serum total protein concentration of the fat than the lean pigs. The differences in serum proteins, cholesterol and lipoproteins between the two strains persisted after the initial difference in weight gain had been abolished by the Aureomycin supplement. The difference in the appearance of the pigs, with persistence of the "long-lean" habitus was still evident. The data show that physical habitus or somatotype affects protein, cholesterol and lipoprotein patterns of the blood, independently of diet, in animals of like species but different genetic strains.

3:00

30. Effects of Fat Ingestion and Heparin Administration on Serum Lipids of Normal, Hypercholesterolemic and Hyperlipemic Subjects

Peter T. Kuo, Claude R. Joyner, Jr. and John G. Reinhold. From the Edward B. Robinette Foundation, Medical Clinic and the Pepper Laboratory, Hospital of the University of Pennsylvania, Philadelphia, Pa.

The effects of fat ingestion and heparin administration on serum cholesterol, phospholipids, neutral fat, and paper electrophoretic serum lipoprotein pattern were investigated in 10 normal persons, 12 hypercholesterolemic and 6 hyperlipemic patients.

Lowering of the neutral fat level, and decrease in both the α and β lipoprotein peaks in the electrophoretic pattern were observed in fasting hyperlipemic patients following heparin injection. These changes were not demonstrated in normal persons and hypercholesterolemic patients. Intravenous heparin did not produce a significant change in the other serum lipid fractions of these patients and normal persons.

Three to 5 hours after fat ingestion, an increase in the mobility and in the height of the β-lipoprotein and the neutral fat zones in the electrophoretic pattern occurred in 9 of the 12 patients with hypercholesterolemia and in all patients with hyperlipemia. The extent of these changes corresponded roughly to the patients' serum neutral fat levels. Normal persons with low postprandial serum neutral fat levels showed little change in the electrophoretic pattern.

Heparin administration to hyperlipemic patients at the height of their post-absorptive lipemia caused a reduction of both the α and β lipoprotein zones, and a marked increase in mobility and spreading of these lipid zones on filter paper, while a significant fall in their serum neutral fat levels was also observed. These effects were less pronounced in hypercholesterolemic patients and were slight in normal subjects.

The apparent increase in height of the β-lipoprotein peak during postprandial lipemia could be caused by excessive "piling-up" of neutral fat particles near the β-lipoprotein zone. The lowering of both the α and β lipoprotein peaks, following heparin injection to a person with post-absorptive lipemia and/or idiopathic hyperlipemia, is at least in part related to the increased mobility and diffuseness of the various serum lipid zones.

3:20

31. Observations Regarding the Effects of Unsaturated Fats

Roger W. Friskey, George D. Michaels and Laurance W. Kinsell. From the Institute for Metabolic Research of the Highland Alameda County Hospital, Oakland, Calif.

Studies carried out during the past several years in normal and abnormal human subjects have demonstrated a predictable and profound decrease in plasma cholesterol and phospholipids during the ingestion of diets containing large amounts of vegetable fat. The mechanism of this effect has been unclear; (1) the cholesterol content of the fat used, (2) the effects of vegetable sterols and (3) the unsaturated fatty acid content have been considered. The changes produced cannot be adequately explained by the cholesterol or vegetable sterol content of the fat used.

Recent studies have shown that the ingestion of high iodine number (unsaturated) vegetable fats results in the usual striking fall in plasma cholesterol and phospholipids. Substitution of a calorically equivalent amount of a highly saturated vegetable fat can result in a prompt and maintained rise in plasma lipids. Some published data suggest that the fatty acid component of cholesterol esters is normally unsaturated. It seems not improbable that a readily available source of unsaturated fatty acids may be essential to normal cholesterol metabolism. This hypothesis is being subjected to experimental evaluation.

3:40

32. Atherosclerosis, Serum Cholesterol and Beta Lipoproteins and the Diet in Three Populations in Cape Town

Ancel Keys, B. Bronte Stewart, John F. Brock, Aileen Moodie, Margaret Haney Keys and A. Antonis. From the Department of Medicine, University of Cape Town, South Africa and the Laboratory of Physiological Hygiene, University of Minnesota Minneapolis, Minn.

Average diets of Cape Province Bantus and Negroes provide 16 and 25 per cent of calories from

fats respectively, while the average diet of the local Europeans resembles that in the U. S. (40 per cent). Emaciation is uncommon and obesity occurs in all three groups. Severe atherosclerosis and myocardial infarction are very rare among the Bantu, fairly frequent among Negroes and very common among "Europeans." There is no such great distinction between the three groups in the incidence of hypertension. In samples of Cape Province men, including 300 of middle age, the distribution, at given age of blood pressures, was similar in the three groups but there were great differences in serum cholesterol. Beta lipoprotein cholesterol, from analysis of paper electrophoresis fractions, in Bantus averaged 52 per cent of that in Europeans of the same age, the Negro male being intermediate. Within each of the three groups, serum cholesterol was directly related to dietary fat intake. A direct relationship between body fatness and serum cholesterol was marked in Bantu, slight in Negroes and absent in Europeans. Serum cholesterol in thin Europeans averaged 45 mg. per cent higher than in fat Bantus of the same age (average 47 years). Data on body type and smoking habits of the three groups are also presented.

4:00

33. The Prevalence of Coronary Artery Disease Among Randomly Chosen Men of Italian and Jewish Origin

Frederick H. Epstein and Ernst P. Boas.† From the Research Department, Sidney Hillman Health Center, New York, N. Y.

We have examined 683 employed men, age 40 and over, chosen at random from a population of 32,000 garment workers in New York City. The frequency of manifest coronary disease, diagnosed from history or electrocardiographic signs, was 7.9 per cent among 232 men of Italian and 15.8 per cent among 372 men of Jewish origin ($P < .01$); these percentages were adjusted to the age distribution of the entire group. Roentgenographic evidence of calcification in the thoracic or abdominal aorta, hypertension, diabetes and obesity were of comparable frequency among Italians and Jews.

The proportion of calories derived from dietary fat was approximately 35 per cent in either ethnic group. The animal fat content of the Jewish diet was 0 per cent higher than that of the Italian diet.

In each quinquennium, we selected ten per cent of the men with the highest cholesterol levels and designated these levels as indicative of hypercholesteremia. Hypercholesteremia, thus defined, occurred among 5.2 per cent of the Italians and 14 per cent of the Jews ($P < .01$). In the small group of hypercholesteremic persons, coronary disease occurred among approximately 25 per cent of both Italians and Jews. Coronary disease was present among 6.4 per cent of Italians and 15 per cent of Jews with normocholesteremia.

A similar picture emerged from a comparison of age-adjusted, mean serum cholesterol levels. Among Italians and Jews with coronary disease these levels were 233 ± 10.8 and 245 ± 6.0 mg. per cent and, in the absence of coronary, peripheral or aortic atherosclerosis, 218 ± 2.8 and 237 ± 2.9 mg. per cent, respectively. Ratios including cholesterol, phospholipid and uric acid provided no additional information concerning ethnic differences.

The predisposition of Jews towards hypercholesteremia fails to account to a large extent for their striking predisposition towards coronary artery disease. While diet and serum lipid patterns no doubt contribute to ethnic differences in the prevalence of atherosclerosis, the present studies point to additional factors, so far unknown.

† Deceased

4:20

34. Inhibition of Cholesterol Synthesis In Vitro By Phenylethylacetic Acid

Daniel Steinberg and Donald S. Fredrickson. From the Laboratory of Metabolism, National Heart Institute, Bethesda, Md.

Cottet and co-workers have recently reported the use of phenylethylacetic acid (alpha-phenylbutyric acid) in the treatment of hypercholesterolemia. Because of promising results obtained in these clinical studies it was felt desirable to explore the possible mechanism of action of this compound.

Rat liver slices were incubated with sodium acetate-1-C^{14} in Krebs-Ringer phosphate medium, pH 7.4, for two hours. At the end of the incubation the total radioactivity in cholesterol, fatty acids, CO_2 and acetoacetate was determined. At concentrations of 4×10^{-3} M, there was striking inhibition of acetate conversion to cholesterol, fatty acids, and acetoacetate, with no inhibition of oxygen uptake. These preliminary results suggest that the effect of this compound on lipid synthesis is not mediated simply through a general effect on oxidative metabolism. Related compounds, α,α diphenyl butyric acid and β,β diphenylethylpropionic acid, likewise inhibit lipid synthesis in a similar manner.

The question of whether the observed inhibition of cholesterol synthesis in vitro entirely explains the effects of the drug on serum cholesterol levels is being examined. Preliminary studies on drug-fed rats (100 to 200 mg. per Kg. per day) show, in agreement with the results of Cottet and co-workers, a small but significant lowering of the serum cholesterol level. The liver concentrations of cholesterol and of coenzyme A were not altered. Further in vitro and clinical studies of the effect of phenylethylacetic acid

and related compounds on lipid metabolism are in progress and will be reported.

4:40

35. Cholesterol Lowering Action of Metal Binding Agents in Man

Henry A. Schroeder, and H. Mitchell Perry, Jr. From the Washington University School of Medicine, St. Louis, Mo.

Curran has reported the enhancement of hepatic cholesterol and fatty acid synthesis from acetate by chromium, manganese (J. Biol. Chem. **210:** 765, 1954) and ethylenediamine tetraacetate (EDTA) (Proc. Soc. Exper. Biol. & Med. **88:** 101, 1955) and its inhibition by vanadium and 8-hydroxyquinoline in rats. Because "abnormal" trace metals are found in American human tissues and might therefore affect cholesterol synthesis in man, calcium EDTA was given intravenously in doses of 3 Gm. per day for 6 to 8 days to 21 human subjects. A prompt fall in plasma total cholesterol occurred, followed by a rise to control levels a few days after the chelator was discontinued. The mean fall was 77 mg. per cent. No signs of hepatic damage were observed. In all but two, the nadir reached was between 120 and 150 mg. per cent. Both of these patients, one with nephrosis secondary to amyloid disease and one with atherosclerosis and angina, developed acute skin lesions of B complex deficiency, rapidly regressing. Orally administered drug given for several months caused similar or less depression at longer intervals in two subjects. When initial values were below 140 mg., no significant changes occurred.

Hydralazine, a metal binding agent with other chemical properties, has been given to over 100 patients whose cholesterol levels were followed at intervals from three days to three years. A similar but less marked fall in total cholesterol occurred in all but six, which was sustained for six months or more. In only 7 of 62 whose control levels exceeded 215 mg. per cent was there a rise after therapy. The mean fall was 44 mg. per cent. Of 46 patients with lower cholesterol levels 20 showed an increase, although the mean change was a fall of 5 mg. per cent. The groups were divided on the basis of length of therapy without demonstrating any differences. Symptoms of arterial insufficiency lessened or disappeared in some individuals but changes were difficult to evaluate in terms of change in cholesterol. When late toxicity to this agent occurred, total cholesterol levels were low. The mechanism of these alterations is obscure but there is no evidence that it depends upon an hepatotoxic effect and may be related to the excretion of one or more trace metals.

5:00

36. Arteriosclerosis in the Intramural and Extramural Portions of Coronary Arteries in the Human Heart

Jos. C. Edwards, Charles Burnsides, Richard L. Swarm and A. I. Lansing. From the Departments of Medicine, Pathology and Anatomy, Washington University School of Medicine, St. Louis, Mo.

Geiringer found that the macroscopic incidence of the mural type of left anterior descending coronary artery was 23 in 100 consecutive autopsies. The vessel was buried 5 mm. or more, at any part of its course. He states that it is quite clear that mural stretches of the left anterior descending coronary branch are only rarely affected by atherosclerosis, in contradistinction to comparable epicardial segments where this is a common finding. He reasoned that a media-like protective action of the surrounding myocardium occurred.

Because of our interest in such factors and the possible relation of local factors in the pathogenesis of atheromata and arteriosclerosis, we investigated the subject. We carefully inspected a total of 276 hearts from unselected autopsies in the Barnes Hospital and St. Louis City Hospital. Arteries that merely dipped deep into myocardium at their terminal branches were not included. Three of the specimens had to be decalcified before sections could be made. There were 15 patients with intramural coronary arteries among 276 consecutive hearts examined post mortem, an incidence of 5.4 per cent. In 16 hearts with intramural coronary arteries, there was appreciable thickness of the myocardium covering the artery and not merely an invagination of epicardium or epimyocardium folded over the vessel. All but two of the intramural coronary arteries exhibited severe atheromata and narrowing of the lumen. The other extramural coronary arteries in these hearts showed atherosclerotic involvement also. Eight of the intramural coronary arteries had marked atherosclerotic involvement, 6 moderate, and 2 had slight changes.

The other extramural coronary arteries in each of the 16 hearts showed some atherosclerotic involvement also. None of the extramural arteries had complete absence of atherosclerotic changes. Eight of them had marked arteriosclerotic narrowing and four of these had thrombi occluding a portion of the vessel. Six of these extramural coronary arteries showed moderate, while two had slight arteriosclerotic changes. Hypertension was present in only two of the patients. Our data does not permit the conclusion that there is any protection from atherosclerotic changes by the covering of a major portion of a coronary artery by myocardium.

TO BE READ BY TITLE

37. Correlation Between Roentgenologic, Clinical and Newer Biochemical Findings in Atherosclerosis

Otto Deutschberger, A. Allen Goldbloom and Harold B. Eiber. From the New York Medical College, Metropolitan Medical Center. (Bird S. Coler Hospital Division), New York, N. Y.

Roentgenograms of 1,000 patients, 50 to 100 years of age were studied. This included a group of 100 normal subjects, 80 to 100 years of age in whom detailed clinical and chemical studies were performed. The methods included serum lipid partitions, S_f lipoprotein molecules, paper electrophoresis, ballistocardiograms, electrocardiograms, ophthalmoscopy and serial pathologic studies.

The lipoprotein molecules (standard S_f 0–12 and S_f 12–400) rise until the age of 65. They attain a plateau or "threshold" and then markedly decline from the age of 80.

Calcification of the aorta increases with age in both sexes. It starts with a steeply ascending curve which begins to flatten at 80 years of age. Calcification of the thoracic aorta is at a higher level in females in all age groups. With a higher degree of calcification, this becomes more apparent.

Conversely, the percentage of incidence of marked widening of the aortic arch is higher in males than in females in comparable age groups. Both reach a maximum in the 70 to 80 age group, followed by a significant decline in incidence in the 80 to 100 year-old group. This is in agreement with the chemical findings and with the suggested hypothesis that atherosclerosis is an active dynamic process, in which widening is active, whereas calcification is an end result.

Furthermore, marked widening, as determined statistically, is usually not associated with marked calcification in any age group, male and female. The converse is also self-evident. Marked widening with moderate calcification is the general rule in the male, within his respective age group. Marked calcification with only moderate widening is typical of the female in a comparable age group. Calcification of the abdominal aorta (200 subjects) and femoral artery (250 subjects) follows a similar pattern of calcification relationship noted in the thoracic aorta. The routine use of anteroposterior views of the thoracic cage is not only inconclusive, but may be misleading. Lateral and oblique roentgenograms of the abdominal aorta are also required; otherwise 50 per cent of abdominal aortic calcifications would be overlooked.

The significance of the relationship of low serum lipid partitions and low S_f lipoprotein molecule values, with marked roentgenologic aortic calcification and microscopic pathologic atherosclerosis in different age groups, appears to be somewhat paradoxic over what had been anticipated at the beginning of this study.

38. Relative Rates of Synthesis of Individual Phospholipides in Aorta, Plasma and Liver of Cholesterol-Fed Rabbits

D. B. Zilversmit and E. L. McCandless. From the Department of Physiology, University of Tennessee, Memphis, Tenn.

Since the specific activity of total phospholipids of atheromatous aortas of cholesterol-fed rabbits was higher than that of plasma it was concluded that plaque phospholipids are synthesized in the vessel rather than deposited from plasma (Circulation **9:** 581, 1954). However, a metabolically inactive phospholipid in plasma might have camouflaged a plasma-to-aorta specific activity gradient. Thus specific activities of individual phosphatides in aorta, plasma and liver were determined. Rabbits fed Purina chow plus 1 per cent cholesterol and 2.8 per cent fat for five months exhibited highly significant increases in concentrations of aortic lecithin and sphingomyelin (3 and 4-fold) but not of cephalin. Plasma cephalins, lecithin and sphingomyelin increased 5, 9 and 12-fold respectively. From P^{32} studies it was concluded that the turnover of aortic phosphatides in atheromatous aortas is increased in proportion to the increase in their concentrations. The fact that the specific activity of aortic lecithin, cephalin and sphingomyelin exceeded that of plasma in nearly all cholesterol-fed animals confirms the earlier evidence that the aorta synthesizes these phospholipids in situ.

39. Is the Cholesterol-Fed Rabbit Choline Deficient?

N. R. Di Luzio, M. L. Shore and D. B. Zilversmit. From the Division of Physiology, University of Tennessee, Memphis, Tenn.

To clarify the controversial role of choline in the genesis of atherosclerosis, the present study was made to determine (1) whether the cholesterol-fed rabbit is deficient in its dietary supply of choline or its precursors and (2) whether choline would have any influence on the altered liver, plasma and aortic phospholipide metabolism of the atherosclerotic rabbit. The method for the assay of choline deficiency is based on the observation that choline administration to choline deficient rabbits stimulates liver phospholipide turnover, but has no effect on the phospholipide metabolism of the normal animal.

The rabbits were maintained on a high cholesterol diet for five months and injected with P^{32}. At this time one half of the group received a single intravenous injection of choline chloride. Six hours later the concentration and radioactivity of tissue phospholipides were determined. Analysis of the specific activity data indicate that choline produced no stimulation of liver phospholipide synthesis in the cholesterol-fed rabbit. Similarly, choline had no effect on the altered tissue phospholipide concentration and metabolism of the cholesterol-fed rabbit.

These data indicate that the cholesterol-fed rabbit is not lacking in its dietary supply of choline or its precursors. In light of this observation, the predominantly negative effect of choline on the prevention and cure of cholesterol-induced atherosclerosis is understandable.

40. The Hypocholesteremic Effect of a Hot Alcoholic Extract of Brain in Hypercholesteremic Patients

Richard J. Jones and O. K. Reiss. From the Department of Medicine, University of Chicago, Chicago, Ill.

Nine patients with coronary artery disease and varying degrees of hypercholesteremia have taken up to 40 Gm. per day of a hot alcoholic extract of mammalian brain for periods of three to eight weeks. All had been followed for long control periods with frequent serum lipid analyses. Each patient sustained a significant fall in total serum cholesterol during the period of cerebroside administration. Mean values during this time were 13 to 26 per cent below the control level. Phospholipid and neutral fat of the serum tended to parallel the changes in cholesterol, but being less marked, the cholesterol to phospholipid ratio fell. Ultracentrifugal data indicated that the beta lipoprotein was consistently depressed during the treatment period, the alpha lipoprotein remaining constant or increasing slightly.

Studies of fecal steroids in animals and patients indicate that the total steroid excretion is enhanced by this material, though the mechanism remains uncertain. Radioisotope studies, employing endogenously labelled C^{14} cholesterol, reveal a significant increase in turnover of serum cholesterol with this material.

41. The Evolution of Arteriosclerosis due to Hypervitaminosis D in Rabbits

Richard Trueheart, George M. Hass, and C. Bruce Taylor. From the Rush Laboratories of Pathology and Surgical Research, Presbyterian Hospital, Chicago, Ill.

Young rabbits on standard diets were given graded doses of viosterol intramuscularly at variable time intervals for one to about 12 weeks. Periodic analyses of serum calcium, phosphate and cholesterol were made. Animals were sacrificed and autopsied at intervals so that a comprehensive microscopic study of sequential effects of hypervitaminosis D on all organs and tissues could be made. These studies showed various stages in development, regression and repair of widely distributed degenerative lesions which were customarily preceded, accompanied or followed by deposition of calcium salts. Mesenchymal elements in special locations were particularly susceptible to these changes while identical elements elsewhere were never involved. Nor was there any apparent relation between tissue changes and serum calcium or phosphate levels. Each affected organ or tissue had its own characteristic relative level of sensitivity and pattern of reaction to a given viosterol regime over a given tissue. Under certain conditions, the degenerative and calcific changes were accompanied by indolent inflammatory reactions. Under other conditions, the changes seemed to occur without any reaction. Under still other conditions, the changes were accompanied or followed by reparative reactions with or without meager signs of inflammation. Certain arterial walls were among the most sensitive tissues, but each arterial system had its own level of susceptibility which varied with the size, structure and function of different branches of the system. The resemblance between these variable and electively distributed processes in vascular walls and those occurring in human arteriosclerosis of the nonatheromatous type is unmistakable and notable without any implication as to identity of etiology.

42. Studies of Free Fatty Acid Release as Evidence of Endogenous Human Lipemia-clearing Activity

Hyman Engelberg. From the Division of Laboratories, Cedars of Lebanon Hospital, Los Angeles, Calif.

Evidence of lipemia clearing activity in the plasma of some normal individuals without the prior injection of heparin has been previously presented. Decreases in optical density were found using mixtures of plasma and a sesame oil substrate. In the present studies release of free fatty acids or of glycerol was determined after incubation of lipemia plasma alone, or of plasma and a coconut oil substrate. The results demonstrate the existence of an endogenous lipolytic mechanism in the blood plasma, indicating that the previously reported optical density decreases were the result of triglyceride hydrolysis.

Parallel studies of free fatty acid release using plasma and serum aliquots substantiate that serum does not usually possess this endogenous lipolytic mechanism. The effect of various enzyme inhibitors on the release of free fatty acid will be presented in order to clarify the nature of the lipolytic enzyme or enzymes. Evidence of the presence of an inhibitor in the serum of one patient has been obtained.

43. A Controlled Study of the Effect of Intermittent Heparin Therapy on the Course of Human Coronary Atherosclerosis

Hyman Engelberg, R. Kuhn, and M. Steinman. From the Cedars of Lebanon Hospital, Los Angeles, Calif.

The injection of adequate amounts of heparin results in a marked reduction of the low density serum lipoproteins and has been reported to retard the development of atherosclerosis in cholesterol-fat fed animals. Evaluation of the results of heparin therapy on the course of human atherosclerosis is therefore important. Studies of its effect upon angina (a subjective manifestation of pre-existing disease which is hard to evaluate) have been contradictory and highly controversial. We felt it was desirable to observe the objective manifestations of progress of the disease in a group of patients with advanced coronary atherosclerosis.

Accordingly, over 200 patients who had each sustained a myocardial infarction in the past were alternately placed into two groups. All patients had a preliminary electrocardiogram, ballistocardiogram, serum cholesterol and ultracentrifugal lipoprotein determinations. One group received 200 mg. of concentrated aqueous heparin, subcutaneously, twice weekly, the minimum believed necessary to produce a substantially decreased average concentration of the low density serum lipoproteins. The other group received 1 cc. of isotonic saline subcutaneously, twice weekly. In all other respects therapy was identical. Fat restriction was not prescribed.

Within the past two years the placebo group of 81 men and 37 women (average age, 61.6 years) received 2,191 months of therapy (average 18.6 months per patient). There were 21 deaths due to cardiovascular disease in this control group. The heparin group of 73 men and 32 women (average age 62.6 years) received 2,067 months of therapy (average 19.7 months per patient). In this group there were four deaths due to cardiovascular disease. The observed difference in deaths is statistically significant ($p = .01$). These results indicate that heparin, in the dosage and manner administered, markedly retards the progress of cardiovascular disease in patients with coronary atherosclerosis.

44. Fat Absorption

H. Necheles, H. Singer and J. Sporn. From the Department of Gastro-Intestinal Research, Medical Research Institute, Michael Reese Hospital, Chicago, Ill.

In normal man and dog, absorption of glucose and of aminoacids is depressed when glucose and gelatin or aminoacids are fed together or when they are fed with fat. Fat by itself depresses absorption of sugar and of aminoacids, but fat absorption itself does not appear to be depressed by other nutrients. It seems that fat has a preferential position with regard to absorption by (1) not being affected by other foods and by (2) depressing absorption of other foods. These findings are of interest when viewed in the light of the theory of chylomicron-induced atherosclerosis.

45. The Diffusion of Egg Yolk Lipid Through the Walls of Arteries in the Dog

Charles A. Woerner. From the University of Louisville School of Medicine, Louisville, Ky.

Dogs were injected intravenously with from 1 to 12 Gm. of egg yolk (dry weight) per Kg. Four hours to three weeks after the last injection of egg yolk, the arteries were fixed in formalin and stained with Oil Red O or by the Rinehart method for mucopolysaccharide.

There was no thickening of the intima of the coronary arteries and no accumulation of lipid in the intima or media of the coronary arteries. In the aorta, subclavian, carotid and iliac arteries the lipid diffused through the intima and media. There were very few foam cells or lipid containing macrophages and only slight intimal thickening. When from 3 to 6 Gm. of egg yolk per Kg. were injected, the lipid was found only in the inner third of the media. Almost all of the lipid droplets were less than 0.4 μ in diameter 24 hours after the injection, but 72 hours after the injection some droplets were 6.0 μ in diameter. When 9 to 12 Gm. of egg yolk per Kg. were injected, the lipid extended into the outer third of the media. The internal elastic lamella did not interfere with the diffusion of the lipid into the media. In the inner third of the media the lipid was found together with the mucopolysaccharide in the accumulations of the ground substance. When fibrous thickenings of the intima were found, the lipid diffused through the thickenings, but no foam cells accumulated. In the larger accumulations of mucopolysaccharide and lipid many of the elastic fibers were fragmented but the same condition was noted in a number of untreated dogs.

46. Epidemiologic Investigation of Group Mortality Trends in Chicago Due to Arteriosclerotic and Hypertensive Cardiovascular Disease

J. Stamler. From the Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago, Ill.

The present study is the initial phase of a projected long-term program of epidemiologic research on morbidity-mortality trends due to the cardiovascular-renal diseases in different population groups in the United States. Breakdown of 1953

Chicago deaths into specific age-race-sex-occupation-income groups reveals the following trends:

In arteriosclerotic heart disease (categories 420, 422, 420 + 422, Sixth Revision, International Statistical Classification of Diseases, Injuries and Causes of Death) men tend to have a higher age-specific death rate than women, confirming the relative immunity particularly of premenopausal women. This relative immunity of women tends to be greater in white than in Negro women of the same age, and greater in employed women (particularly professional and white collar) than in housewives of the same age-race group. Negro males tend to have a higher age-specific death rate than white males. Laborers tend to have a higher death rate than other men in their age-race group. White males, from census tracts with the lowest median income, tend to have a higher age-specific death rate than white males from other census tracts.

In hypertensive cardiovascular disease (categories 440–447) Negroes tend to exhibit higher death rates than whites of the same age-sex group, in confirmation of previous observations. Laborers tend to exhibit higher death rates than other men in their age-race group. Housewives tend to exhibit higher death rates than employed women in the same age-race group.

These mortality trends appear to differ markedly from those recently reported from Europe. Further work is essential to extend and verify these findings, to investigate factors responsible for observed groups differences and to ascertain their bearing upon current concepts concerning etiology and pathogenesis of these diseases.

47. Patterns of Restitution of Plasma Cholesterol Levels after Acute Hemorrhage in Chicks

Simon Rodbard. From the Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago, Ill.

Mechanisms of regulation of the plasma cholesterol level were studied by determining the rate of its recovery after acute withdrawal of one-third of the estimated blood volume by cardiac puncture in chicks. Hematocrits fell within 5 hours from 20 to 30 per cent, returning to control values in 7 days. Chicks on a normal mash diet showed a fall in plasma cholesterol from 120 to 80 mg. per cent in 6 hours, returning to normal at 30 hours, and rising significantly above normal at the end of 7 days. Chicks receiving intramuscular injections of 1 mg. estradiol daily showed a fall in 6 hours which persisted for one week. Chicks on a mash diet supplemented with 2 per cent cholesterol and 5 per cent oil (2 CO) showed the 6 hour fall, with a tendency to return to the original level at one week. Chicks on a combination of 2 CO plus estradiol had a recovery pattern essentially like birds on estrogen. The latter three groups showed a spontaneous marked reduction in food intake, to less than half of the control values.

The longer delay in restitution of plasma lipids in estrogen treated chicks may be related to the relative rates of mobilization or synthesis of cholesterol in the two states.

48. Hyperlipemia and Pancreatitis Produced by Ethionine

David Adlersberg and Chun-I Wang. From the Departments of Medicine and Chemistry, The Mount Sinai Hospital, New York, N. Y.

Acute pancreatitis may be associated with transient hyperlipemia of the plasma. Conversely, idiopathic hyperlipemia seems to represent a predisposing factor for relapsing pancreatitis.

Ethionine, a methionine antagonist, was used to produce pancreatitis in rabbits. The investigation so far included 5 male and 4 female rabbits. The males were injected daily intramuscularly with ethionine in doses of 400, 300 and 200 mg. for 7 days. All of the animals developed lactescence of the plasma with increase in neutral fat and total lipid. Total cholesterol reached values of 360, esterified cholesterol 238, phospholipids 326 and total lipids 1220 mg. per cent. All of the animals had normal blood sugar levels. At autopsy, animals treated with higher doses of ethionine exhibited more severe pancreatitis and more marked fatty livers than those treated with smaller doses. In two animals observed after recovery from pancreatitis, the plasma and total lipids were elevated for 7 days.

All four female animals receiving 200 mg. of ethionine daily died in 4 to 6 days. At autopsy, the pancreas of the females showed little evidence of inflammation and the fatty degeneration of the liver was less marked than in the males. There seemed to exist sex differences in the tolerance and effects of ethionine in the rabbit.

49. Experimental Production of Skin, Tendon and Bone Xanthoma

Chun-I Wang, Lotte Strauss and David Adlersberg. From the Departments of Medicine and Pathology, The Mount Sinai Hospital, New York, N. Y.

One hundred and twenty rabbits were fed cholesterol-treated Purina Chow (approximately 1 Gm. cholesterol daily). Of these, 33 animals were observed for 3 to 6 months (group I), 19 for 6 to 9 months (group II) and 4 longer than 9 months (group III). Skin xanthomata were observed in 3, about one-tenth of the animals of group I, in 8, two-fifths of those in group II and in all 4 animals of group III.

Grossly, the xanthomatous skin lesions began as small reddish-yellow papules and nodules over the paws, between the toes and over the heels. The skin of the soles of these animals was thickened and cracked. The lesions developed into nodes varying in size from 0.5 to 1.5 cm. in diameter. In one instance xanthoma of the limbs assumed the proportion of a tangerine (6 cm. in diameter). Not infrequently, the nodes opened and discharged cheesy material which had a high cholesterol concentration (1 to 2 per cent). In four animals marked thickening of the knees and/or ankles was noted. Roentgen studies of these joints disclosed considerable thickening of both the bones and the soft tissues. In two instances pathologic fractures developed. Histologically, the fully developed lesions localized in the skin, tendons and bones revealed the typical picture of xanthoma; the early skin lesions which were not visible to the naked eye showed occasional isolated or nests of foam cells in the upper corium and in perivascular and perineural spaces in the deep corium.

50. Electrophoretic and Lipoprotein Analysis in Familial Primary Systemic Amyloidosis

John G. Rukavina, Walter D. Block and Arthur C. Curtis. From the Department of Dermatology and Syphilology, Medical School and the Institute of Industrial Health, University of Michigan, Ann Arbor, Mich.

A genetic isolate consisting of 66 members of a family with a history of primary systemic amyloidosis has been investigated. Clinical investigation on these patients included neurologic examination, liver function tests, skin biopsies and bone marrow aspirations. Serum electrophoretic studies were carried out on the 66 patients. Lipoprotein determinations were done on 33 of these patients, using the ultracentrifugation technic. The inheritance characteristics of the disease were also studied.

Results of the electrophoretic studies showed that 29 of these subjects had distinctly atypical patterns in the α_2-globulin region. In 15 cases these patterns were characterized by the presence of an atypical peak migrating between the α_2 and β globulin fractions. In 14 cases the patterns were characterized by poor resolution in the α_2-globulin area. Significant quantitative abnormalities in the various protein fractions could not be demonstrated.

Lipoprotin analyses on these sera indicated abnormalities in 29 of the 33 cases studied. Significant elevations were found in all the lipoprotein fractions, but most consistently in the −S 25–40 and 20–25 fractions, corresponding to α_2 and β globulin respectively. These increases indicate that at least a part of the atypical serum protein fraction consists of lipoprotein.

A definite correlation was found between the existence of clinical signs and symptoms of the disease and the atypical serum protein pattern. Similarly, the existence of clinical signs and symptoms could be correlated with abnormalities in lipoprotein levels. Consideration of the genetic data concerning the disease in this family indicates a dominant form of inheritance.

51. Further Studies on Dietary Factors Affecting Plasma Lipid Levels in Humans

J. M. R. Beveridge, W. F. Connell and G. Mayer. From the Departments of Biochemistry and Medicine, Faculty of Medicine, Queen's University, Kingston, Ontario, Canada.

Three dietary experiments have been performed in which 36 to 49 medical students and staff participated as experimental subjects. In each study, all participants consumed the same homogeneous formula diet for eight days. The group was then divided into five, on the basis of plasma cholesterol values determined on the fourth day. One section remained on the original diet for a further eight days. The others received diets varying in respect of the level and nature of the fat moiety. Protein supplied 16.9 per cent of total calories.

In the first experiment, 37 subjects ingested a diet providing 58.5 per cent of calories as corn oil. During the initial period the plasma cholesterol dropped 31.2 per cent. Those continuing on corn oil displayed a further insignificant decrease. The others, receiving diets high in beef dripping, chicken fat, lard and butter showed increases of 8.6, 8.8, 12 and 25.2 per cent respectively..

In the second experiment, 49 subjects consumed a fat-free diet for eight days. The plasma cholesterol decreased 21.4 per cent. Those continuing on the fat-free diet showed little further change. Those ingesting 20 and 60 per cent of calories as corn oil showed further decreases of 10 and 13.8 per cent respectively. By contrast, those receiving diets providing 20 and 60 per cent of calories as butter fat showed increases of 5.2 and 17.5 per cent.

In the third experiment, 36 subjects ingested a diet for eight days in which butter fat provided 60 per cent of the calories. The plasma cholesterol level remained essentially constant, and did not change significantly in those continuing on this diet for a further eight days. The composition of the fat moiety in the remaining groups in terms of per cent calories derived from butter fat and corn oil, respectively were: 45 to 15; 30 to 30; 15 to 45 and 0 to 60. The decreases in plasma cholesterol values were, respectively, 2.6, 15.2, 25 and 28.2 per cent. In addition to other conclusions, these studies demonstrate that in animal fat, a factor or factors act to elevate plasma cholesterol levels and a factor or factors act in corn oil to depress plasma cholesterol levels.

52. Effect of Intermittent Fatty Meals on Pulmonary Arteriosclerosis Induced by Thromboembolism in the Rabbit

W. A. Thomas, R. M. O'Neal and K. T. Lee. From the Department of Pathology, Washington University, St. Louis, Mo.

In recent years a number of investigators have produced fibrous intimal thickening of small pulmonary arteries in rabbits by repeated intravenous injections of blood clot. Absence of fat in the lesions has been reported in almost all instances, although the lesions are otherwise characteristic of pulmonary arteriosclerosis.

It is possible that the absence of fat in the sclerotic arteries is related to the paucity of fat in the rabbit's diet. Hence, a series of experiments were planned to determine the effect of fatty meals on thromboembolic-induced pulmonary arteriosclerosis in rabbits. Rabbits receiving weekly injections of blood clot intravenously have been divided into groups and given in addition, (by means of transoral gastric intubations) melted butter ("butter-clot" group) or melted oleomargine ("oleomargarine-clot" group) or warm water ("water-clot" group).

Microscopic sections of lungs from 18 rabbits (8 from the "water-clot" and 5 each from the other two groups) have been examined, and more animals are currently being studied. Fibrous intimal thickening in the pulmonary arteries has been found in all groups, and results to date indicate that the severity of the lesions is greater in the animals receiving supplementary oral lipids. However, small but definite quantities of fat have been demonstrated in occasional arterial lesions in approximately one half of the animals in all groups. The unexpected presence of fat in the pulmonary arterial lesions of the "water-clot" group is of special interest.

Similar pulmonary arterial lesions have not been observed in control rabbits receiving only intravenous saline and intragastric butter. Additional experiments are in progress, designed to determine the significance of observations made in these initial experiments.

53. An Evaluation of the Serum Lipids in Human Atherosclerosis: An Interim Report

J. C. Paterson, B. R. Cornish and E. C. Armstrong. From the Clinical Investigation Unit of Westminster Hospital, Department of Veterans' Affairs and the Collip Medical Research Laboratory, University of Western Ontario, London, Ontario, Canada.

As reported to this society last year, we are attempting to assess the importance of certain serum lipids, measured serially during life over long periods, with the actual amount of atherosclerosis found at death and autopsy. The serum lipids examined are the total cholesterol, the cholesterol-phospholipid ratio, and the S_f 0–12, 12–20, 20–100 and 100–400 classes of lipoproteins. The degree of atherosclerosis is assessed at autopsy in the abdominal aorta and in the coronary, cerebral and femoral arteries. These assessments are made by crude morphologic grading, by measuring the thickness of the largest plaque in each vessel, and by determining chemically the amount and concentration of lipid and of calcium deposited in each vessel. Thus, a comparison is made of six different serum lipid fractions with the degree of atherosclerosis assessed in six different ways, in four types of arteries, a total of 144 separate analyses.

The project was instituted 30 months ago on 700 patients who are permanently confined to hospital, 600 of them being psychotic. To date, 50 of these have died and autopsies were performed. In only 3 of the 144 statistical analyses made on the data from these cases has any significant relationship been found between the antemortem serum lipid levels and the degree of atherosclerosis: (1) an elevated cholesterol-phospholipid ratio in cases with severe coronary sclerosis as measured by crude morphologic grading, (2) an elevated cholesterol-phospholipid ratio in cases with severe femoral artery sclerosis as measured by the lipid concentration, and (3) an elevation of the S_f 0–12 class of lipoproteins in cases with severe coronary sclerosis as measured by crude morphologic grading. All other analyses showed no relationships. The project is continuing.

54. Aortic Medial Lesions in Repeatedly Bled Rabbits

John J. Spitzer and V. Tompkins. From the Division of Laboratories and Research, New York State Department of Health, Albany, N. Y.

Male rabbits aged two to four months responded to hemorrhage with lipemia. Within a few days, lesions of the aorta were seen in bled and sham-punctured animals more often than in controls. The lesions were located in the ascending portion and arch of the aorta and rarely in the thoracic portion. Fundamental changes which occurred in the inner media consisted of straightening and hyperchromatism of elastic fibers. The fibers were separated at the lateral edges of the lesions by increased ground substance, generally cell-poor. As a result, the aorta appeared opaque with peripheral elevation and central depression. When confluent the aortic surface was irregular, pitted and furrowed. Lesions showed no disposition to involute or heal, though calcification became more prominent with time.

Despite alterations in fat and carbohydrate metabolism the lesions were fat free. There had been visible lipemia, greatly elevated S_f 20–100 lipoproteins, and changes in clearing factor mechanism as previously reported. Blood sugar was in

creased in bled animals and the increase could not be prevented by priscoline.

Force feeding of oil did not result in deposit of sudanophile material in lesions. Thorium dioxide did not localize in the vicinity. Reinjection of blood cells or plasma did not prevent lesions nor did heparin protect against them.

55. A Comparative Study of Blood Fats in Atheromatosis

Paul B. Roen, Ernest W. Townsend and John W. Perry. From the Clinic for the Study of Arteriosclerosis, Hollywood Presbyterian Hospital, Los Angeles, Calif.

Quantitative determinations of various blood fats in the serum of "normal" individuals and in patients with proven atherosclerotic lesions disclose apparent lack of correlation among the results of individual tests now in use. No single test in our series is an index of the extent of atherosclerosis and the exact relation between human atherosclerosis and the lipids is still to be defined. Therefore, for a true picture of lipid metabolism all possible information should be obtained.

In all cases the amounts of total lipids, total cholesterol, and total phospholipids are obtained together with ratios and units of turbidity; electrophoretic patterns are studied by the simple method of Spaeth; the ultracentrifuge determinations were performed in some cases; and chylomicrons are photographed in a test developed in our own laboratories.

Photographs of blood serum samples are taken after a fast of 12 hours and, again, 6 and 24 hours after a test meal which includes a given amount of fat. As most of our patients are on a low lipid diet, photographs of the fasting pattern serve, not only to ascertain the body's ability to withdraw fats from the blood stream, but also as a check upon the strictness with which the patient has adhered to his prescribed diet.

Reliance should not be placed on a single test of blood fats, but as many tests as are practicable should be employed to round out a composite picture. Spaced serial examinations give added information concerning lipid metabolism in individual patients.

56. Spontaneous Atherosclerosis in the Rat

Manuel René Malinow, David Hojman and Amanda A. Pellegrino. From the Pabellón de Cardiología Inchauspe, Policlinico Ramos Mejia, Buenos Aires, Argentina.

Autopsies were performed on 30 male white William strain rats, weighing between 230 and 425 Gm. The animals had been maintained on a mixed standard diet and were sacrificed when at least 15 months old. The aorta and the proximal portion of its primary branches (i.e., intercostal, mesenteric, iliac arteries), the heart and the kidneys were studied microscopically; an average of 350 arterial sections were observed in each rat. The following microscopic arterial lesions, singly or combined, were found in 16 animals: (a) endothelial and/or subendothelial infiltration, sometimes extending into the media, of a sudanophilic, Lieberman-positive material; (b) proliferation of endothelial and/or subendothelial (?) cells forming tiny protruding plaques. Just a few arterial sections showing these changes were seen in a single rat; a preferential localization in any arterial territory was not demonstrated. Although extensive inflammatory changes were observed in most rats, no correlation was found between an inflammation in the arteries (or in any other organ) and the atherosclerotic changes. The heart to body weight ratio was not elevated; blood cholesterol levels averaged 96 mg. per cent (range 90 to 127); urea nitrogen values averaged 36 mg. per cent (range 10 to 78) probably due to the common occurrence of chronic pyelonephritis in the present series.

57. Chromatographic Separations of Biosynthetic Sterols from Rat Skin and Liver

Ivan D. Frantz, Jr., Veronica M. Anderson and Ann G. Davidson. From the Cardiovascular Research Laboratory, Department of Medicine, Medical School, University of Minnesota, Minneapolis, Minn.

We have found it possible to obtain satisfactory separations of some compounds related to cholesterol by chromatography on silicic acid. The silicic acid is mixed with half its weight of "Supercel." The free sterols are placed on the column and are eluted with undiluted benzene.

When applied to skin sterols, this method effected the separation of lathosterol from cholesterol. Another "fast-acting" sterol, present in smaller amounts than lathosterol, was also separated. This compound travels ahead of cholesterol. It appears to be unseparated from cholesterol by a previously described method, in which the azoyl esters of the sterols are chromatographed.

We subjected the digitonin precipitable sterols of liver slices to chromatography, after incubation of the slices for various lengths of time in C^{14}-labeled acetate. After incubation for three hours, 95 to 99.5 per cent of the radioactivity emerging from the column coincided in position with cholesterol. The higher percentage was found when no carrier acetate was added during the incubation. Two other peaks of radioactivity, coinciding closely in mobility with lathosterol and with the unidentified skin sterol mentioned above, also appeared. A fourth peak of radioactivity emerged ahead of the latter.

After shorter periods of incubation, as much as 40 per cent of the radioactivity was associated with compounds other than cholesterol. After incubation

for 7 minutes, more than 30 per cent moved at the same rate as lathosterol, and additional peaks appeared.

Previous reports have indicated that cholesterol is synthesized rapidly by skin. Under our experimental conditions, most of the radioactivity of the non-saponifiable, digitonin precipitable fraction of skin proved to be not associated with cholesterol. An exceedingly complex chromatographic pattern was obtained, implying the existence of many unidentified compounds.

58. The Relationships Between Arterial and Renal Injury and Diet in the Production of Atheromatous Lesions in the Coronary Arteries of the Rat

Robert Wissler, Robert Allen, Richard Moy and William Bradford. From the Department of Pathology, University of Chicago, Chicago, Ill.

Previous chronic experiments in this laboratory have indicated that the combined administration of antikidney serum (AKS), desoxycorticosterone acetate (DCA) and sodium chloride (NaCl) approximately doubles the incidence of coronary atherosclerosis in the rat as compared to the incidence of lesions observed with diet alone.

Recent acute experiments with adult male rats fed rations high in animal lipid have confirmed the coronary atherogenic effect of this combined treatment of the rat, but no lesions developed acutely when either the DCA or AKS was omitted. However, hypercholesterolemia of approximately comparable degree was observed when only AKS and NaCl were administered to the rat.

When the level of dietary protein or lipid was varied over a wide range in adult male rats receiving AKS followed by DCA and added NaCl, coronary atheromatous lesions and marked elevations in serum cholesterol and lipid phosphorus levels were found in animals receiving either a high fat, high choline, low protein ration or a low fat, low choline, high protein ration.

On the other hand a low protein, low fat, high choline ration administered to rats receiving the combined AKS, DCA, NaCl treatment resulted in less elevation of the serum cholesterol and lipid phosphorus concentrations and no lesions were observed in the coronary arteries.

A ration high in lipid, protein and choline produced even more severe elevation in the serum cholesterol (SC) without a comparable rise in lipid phosphorus (LP), when this dietary treatment was combined with the disturbance in lipid metabolism resulting from AKS, DCA and NaCl treatment. This resulted in a marked rise in the SC to LP ratio and a high incidence of coronary atheromatous lesions.

These results will be contrasted with the effects of variations of these same diet ingredients upon the SC to LP ratio in animals receiving dietary treatment alone. The effects of these various treatments upon the connective tissue of the arterial wall will be illustrated and the experimental results will be related to the problem of the pathogenesis of atherosclerosis in man.

59. The Effect of Epinephrine Administration upon Blood Lipids

Alex Kaplan and Mary Gant. From the Department of Biochemistry, Medical Research Institute, Michael Reese Hospital, Chicago, Ill.

Normal dogs in the postabsorptive state were injected subcutaneously with aqueous solutions of epinephrine hydrochloride or with suspensions in oil of the free base. Serum lipid concentrations were measured at various time intervals after the injection. The administration of 0.1 mg. per Kg. of aqueous epinephrine solution had no perceptible effect in 5 hours upon serum lipid levels. The concentrations of esterified fatty acids, phospholipids and total cholesterol were about 20 per cent above the preinjection level, 24 hours after the hormone administration. When the hormone injection was repeated at the 5 hour interval, the rise in lipid concentration 18 hours later approximated 30 per cent.

The subcutaneous injection of a single dose of slow-acting epinephrine (1.0 mg. per Kg. in oil) produced a hyperlipemia within 24 hours that subsided by the second or third day. The average rise in the serum lipids of 7 dogs treated in this manner was 44 per cent for esterified fatty acids, 40 per cent for phospholipids, 22 per cent for cholesterol and 100 per cent for triglycerides; the greatest fluctuations in response were encountered with the triglycerides. A hyperlipemia was maintained for a week in three dogs by the daily injection of 1.0 mg. per Kg. of epinephrine in oil for seven consecutive days. The effect of epinephrine administration upon the blood lipids of other species is being investigated.

60. Thorazine-Rauwolfia Combination in the Treatment of Senile Agitation, Hypertension and Neuropsychiatry

Harold B. Eiber. From the New York Medical College, Flower Fifth Avenue Hospitals, New York, N. Y.

For the past 24 months various combinations of Thorazine (chlorpromazine) and *rauwolfia serpentina* have been administered to 250 ambulatory patients. These individuals suffered from senile agitation, essential hypertension and various neuropsychiatric disorders. Although these conditions have been treated in the past with *rauwolfia serpentina* or Thorazine separately, there have been no published reports of the use of a combination of the two agents.

Senile agitation is frequently made worse by barbiturates and amphetamines. The Thorazine-rauwolfia combination improved more than 80 per cent of the patients. Essential hypertension, in the young or the aged, was controlled in almost 100 per cent of the mild cases, 70 per cent of the moderate cases and 60 per cent of the severe cases by this combination. Various neuropsychiatric disorders including schizophrenia, depressive states, severe menopausal anxieties, anxiety neurosis and spastic colitis were controlled in more than 80 per cent by use of the combination.

In all instances, therapy was administered orally. None of the patients required hospitalization. In contrast to the use of combinations of other antihypertensive agents for essential hypertension, there were no side effects and therapy was instituted in the office. There were no evidences of jaundice or other toxic manifestations. Duration of effect of each dose was approximately six hours and none of the patients exhibited any acute hypotensive symptoms. There appeared to be no significant difference between the whole root of *rauwolfia serpentina* and one of its alkaloids, reserpine. Therefore, it is felt that the Thorazine-*rauwolfia serpentina* combination is an effective therapeutic agent in the control of senile agitation, essential hypertension in the young or aged and in various neuropsychiatric conditions.

61. The Hypertensive Ulcer

F. Martorell. From the Instituto Policlinico, Barcelona, Spain.

In some cases of hypertensive disease, painful ulcers appear on the anterolateral aspect of the leg. In 1945, I published the first four cases. Later, several papers confirmed the existence, etiology and clinical characteristics of this hypertensive ulcer, termed "Martorell's Syndrome" by some authors.

The ulcer is due to ischemia caused by obliterating lesions of the small arterioles. These lesions are similar to those found in other localities in essential hypertension. The most common changes are an increase in the thickness of the arteriolar wall and a decrease in the diameter of the lumen. The lesions are specific to hypertensive disease, with subendothelial hyalinosis in some cases, or thickness and an increased number of nuclei in the media in others.

The lesion may have been initiated as the result of slight local trauma or even without it. Usually, the first symptom is a painful red patch in the skin, which soon becomes blue and purpuric. Afterwards, superficial necrosis develops and finally ulceration appears, often bilateral and symmetrical. The ulcer is located on the anterolateral aspect of the leg at the union of the lower and middle thirds. An ulcer may be on one side and a simple pigmented spot on the other. The ulcer becomes sensitive and painful and the pain is not relieved by bed rest. No history of thrombophlebitis exists and no varicose veins are found. The dorsalis pedis arteries are palpable. The diagnosis of hypertensive ulcer is made when ulceration, as described above, coincides with diastolic arterial hypertension in the arms and arterial hypertension in the legs, without any arterial occlusion or disturbance of the venous circulation.

62. Atherosclerosis Obliterans of the Abdominal Aorta

Joseph B. Wolffe. From the Department of Medicine, Valley Forge Heart Institute and Hospital, Fairview Village and Wolffe Clinic, Philadelphia, Pa.

A variety of pathologic conditions have been described as "Leriche Syndrome." Among them are traumatic arteritis, embolization of the abdominal aorta, thrombosis in situ, neoplastic infiltration with obstruction and atherosclerosis with constricting cicatrical tissue and/or thrombosis.

Our discussion is limited to atherosclerosis obliterans involving the abdominal aorta. Attention is called to the importance of a simple roentgenologic survey of the abdominal aorta which, if correlated with symptomatology, physical findings and oscillometry, should make the diagnosis of this rather common condition comparatively easy. The therapy consists of the prolonged use of intravenously administered pancreatic extracts, diethyl ether and coenzymes.

63. Lumbar Sympathectomy for Arteriosclerosis Obliterans

Roger F. McNeill and Alexander Blain, III. From the Alexander Blain Clinic, Detroit, Mich.

Lumbar sympathectomy for symptomatic arteriosclerosis obliterans has become increasingly popular during the past decade. In 1949 we presented the rationale and results of this operation before this society. However, indications still remain controversial and the reports of results from different clinics vary. The present report is based on our experience with 74 lumbar sympathectomies done for symptomatic arteriosclerosis obliterans in the past seven years. Our results are analyzed and the present status of this operation is evaluated. Particular emphasis is placed upon selection of patients from the older age groups.

64. The Effect of Heparin on Serum Lipoproteins of Normal and Atherosclerotic Subjects

Bernard A. Sachs and Paxton Cady. From the Medical Division, Montefiore Hospital, New York, N. Y.

The effect of 100 mg. of heparin sodium administered intravenously on serum lipoproteins, as meas-

ured by paper electrophoresis, was studied at intervals for 3 hours in 10 normal subjects and 12 patients with atherosclerosis. Five subjects were studied after a placebo was administered intravenously. These two changes were noted: the shift of β or β-α-2 lipid band toward α-1 ("lipoprotein shift") and the clearing of the band between the point of application of the serum and β globulin ("clearing of neutral fat").

Only 2 of the 10 normal subjects exhibited the lipoprotein shift and this was slight. In contrast, 8 of 12 atherosclerotic subjects exhibited this shift and two others had equivocal changes.

Clearing of neutral fat occurred in 3 normal subjects and in 8 atherosclerotic patients. Three of these did not exhibit an accompanying lipoprotein shift. The five placebo runs exhibited no change. The differences observed in lipoprotein changes, following heparin administration, may provide another method for distinguishing the normal from the abnormal lipid metabolism of atherosclerosis.

65. The Sulfatase and Beta-Glucuronidase Activities of Human Arterial Tissue

M. Dyrbye and J. E. Kirk. From the Division of Gerontology, Washington University School of Medicine, St. Louis, Mo.

Determinations were made by the method of Huggins and Smith of the phenol sulfatase activity of homogenates prepared from 37 samples of human aortic tissue. The average liberation of p-nitrophenol from p-nitrophenylsulfate valued 1.8 μg. per Gm. wet tissue per hour. A significant tendency was observed for the sulfatase activity to decrease with the age of the individuals from whom the samples were derived. Thus the quantity of p-nitrophenol liberated averaged 3.0 μg. per Gm. per hour for the subjects aged 3 to 39 years and only 1.3 μg. per Gm. per hour for 65 to 75 year old individuals. In a limited number of experiments, comparative measurements were made of the sulfatase activity of the aorta, pulmonary and coronary arteries. The average sulfatase activity of the pulmonary artery (N = 5) was found to be 1.66 times that of the aorta, whereas the mean activity of the coronary artery (N = 5) was only 0.71 times that of the aortic samples.

Similar determinations of the β-glucuronidase activity of aortic homogenates were carried out by the procedure of Talalay, Fishman and Huggins. The measurements revealed a mean liberation of 67 μg. of phenolphthalein from phenolphthalein glucuronidate per Gm. wet tissue per hour (N = 58). No definite correlation was noted between the age of the subjects and the glucuronidase activity. The enzyme activity of the pulmonary artery (N = 5) and coronary artery (N = 8) averaged 1.06 and 0.80 times, respectively, that of the aortic homogenates.

66. Some Physical and Chemical Properties of the Aorta and the Relation to Minimal Arteriosclerosis

Howard L. Gottlieb. From the Bjorksten Research Foundation, Madison, Wis.

Technics have been developed in our laboratory to study physical properties of the descending thoracic segments from humans, swine and rats. At the same time, classical histochemical technics have been modified to permit chemical and morphologic studies of the identical specimens. These technics have been applied to tissue in the loci of minimal arteriosclerotic lesions and in morphologically non-sclerotic tissue to delineate possible mechanisms for the initiation of lesions.

From these studies a new hypothesis for the histogenesis of atherosclerosis and other arteriopathies has been developed and critically examined. Although emphasizing the role of the artery in the initial phase of lesion development, agreement with factual data of other investigators has been found. This hypothesis offers a useful basis for clinical investigation of several arteriopathies.

67. Pituitary and Adrenal Relationships to Cholesterol Metabolism in the Rat

M. C. Schotz, G. M. C. Masson and A. C. Corcoran. From the Research Division of the Cleveland Clinic Foundation and the National Heart Institute, National Institutes of Health, Cleveland, O.

The relationships of pituitary and adrenal cortical functions to serum cholesterol concentration are obscure, since these vary in different studies and in different species. Furthermore, associations between serum cholesterol concentrations and changes in hepatic synthesis have been little studied.

This report deals with observations in normal, adrenalectomized and hypophysectomized rats, given desoxycorticosterone or cortisone. Incorporation in hepatic cholesterol of intravenously injected C^{14} acetate was used as the measure of cholesterol synthesis and was determined simultaneously with serum total cholesterol.

Adrenalectomy had little effect on either serum cholesterol or hepatic synthesis. Treatment of adrenalectomized rats with desoxycorticosterone had no effect on serum cholesterol, although hepatic synthesis was increased; cortisone, on the other hand, augmented both functions.

Since the observed effects of cortisone might depend on changes in a hypophyseal or hypophyseal-mediated function (e.g., that of the thyroid), observations were made in cortisone-treated, hypophysectomized rats. These animals demonstrated large increases in both serum cholesterol and hepatic synthesis; both effects increased further with prolongation of cortisone treatment.

The data show that cortisone, and, in some degree,

desoxycorticosterone, increased hepatic cholesterol synthesis in adrenalectomized and in hypophysectomized rats. These effects are independent of a hypophyseal or hypophyseal-mediated function. There is a general, but not obligatory, association between increased hepatic synthesis and increased serum cholesterol concentration. The possibilities of participation of a renal mechanism and of a direct hepatic effect of cortisone, demonstrable in vitro, are under evaluation.

68. Progesterone and Alpha Tocopherol in Experimental Epinephrine-Thyroxine Arteriosclerosis and in Cholesterol-Induced Atherosclerosis.

Y. T. Oester, Oscar F. Davis and Bernard Friedman. From the Department of Pharmacology and Experimental Therapeutics, Stritch School of Medicine of Loyola University, Chicago, Ill.

A high incidence (89.5 per cent) of a severe degenerative aortic sclerosis, essentially of the tunica media, is produced in rabbits by using epinephrine and thyroxine, following the method previously reported by us. The lesions are rapidly induced in 15 days or less. Similarly, an essentially intimal atherosclerosis is induced in rabbits treated for 20 days or less with intravenous and subcutaneous injections of cholesterol suspensions. Alpha tocopherol was studied in these scleroses because reports from Canadian and European sources have indicated that α tocopherol produces improvement in clinical atherosclerosis. The reports of low β lipoprotein blood levels in young females, as well as low S_f 10–30 Gofman fractions in pregnancy led to the investigation of the effects of progesterone on these scleroses.

Five different groups of rabbits, 8 to 19 per group, were given the epinephrine-thyroxine regimen which produces the medial arteriosclerosis. In addition, each group received one of the following agents by subcutaneous injection: group 1 received progesterone, 50 mg. per day; 2, progesterone, 75 mg. per day; 3, α tocopherol, 100 mg. per day; 4, α tocopherol, 200 mg. per day and 5, α tocopherol, 600 mg. per day. None of these groups demonstrated any significant differences in incidence or severity of the induced medial sclerosis when compared to the control group of epinephrine-thyroxine alone. Three different groups of rabbits, 6 to 14 per group, were given the cholesterol regimen which produces the intimal atherosclerosis. In addition, each group received one of the following agents by subcutaneous injection: group 1 received progesterone, 75 mg. per day; 2, α tocopherol, 200 mg. per day and 3, α tocopherol, 600 mg. per day.

The group of animals receiving 75 mg. per day of progesterone exhibited a much lower incidence of the intimal aortic sclerosis than the other two groups or the control group receiving only cholesterol. The incidence in the progesterone group was 23 per cent, 6 in a total of 13 animals, while the control group had an incidence of 71.8 per cent, 23 in a total of 32 animals.

69. Cholesterol Synthesis in Hypercholesterolemic Rabbits

Leon Hellman, R. S. Rosenfeld, Chun-I Wang, Ruth Loevinger and David Adlersberg. From the Sloan-Kettering Institute for Cancer Research and the Mount Sinai Hospital, New York, N. Y.

Cholesterol synthesis from C^{14} labeled sodium acetate has been studied in normal and hypercholesterolemic rabbits. Three groups of animals were used: normal (plasma cholesterol, 46 mg. per cent), hypercholesterolemic due to cholesterol feeding (cholesterol, 682 to 1984 mg. per cent) and hypercholesterolemic due to cholesterol feeding plus cortisone (1926 to 2284 mg. per cent). The radioactivity of plasma free cholesterol in the normal group was at its highest value with the earliest sample taken one day after the administration of 19 μc. of acetate per animal and then declined with $T\frac{1}{2}$ = 10 days over the period of observation of 30 days. Ester cholesterol specific activities were approximately 50 per cent higher than those of the free and declined at a similar rate. The cholesterol of the rabbit erythrocyte was in isotopic equilibrium with the plasma free cholesterol. The specific activity of the plasma cholesterol in the hypercholesterolemic groups of animals was one-tenth or less than that of the normal group. Since the cholesterol levels in the hypercholesterolemic animals exceeded those of the normal by ten-fold or greater, equivalent total quantities of plasma cholesterol could have been synthesized from acetate in the hypercholesterolemic group and the dilution factor could account for the lower specific activities observed. A net reduction in cholesterol synthesis as a result of the hypercholesterolemia may also explain these findings. A similar reduction in specific activity was observed in the cortisone-treated hypercholesterolemic animals.

SPECIAL ANNOUNCEMENTS

AMERICAN SOCIETY FOR THE STUDY OF ARTERIOSCLEROSIS

ANNUAL MEETING

GUEST LECTURER:

Sunday, November 5,
Luncheon 12:00 Noon

W. C. Hueper, M.D., National Cancer Institute, Bethesda, Md.

THE RELATIONSHIP BETWEEN ARTERIOSCLEROSIS AND CANCER

COCKTAIL PARTY:

Sunday, November 5
6:30 P.M.
Sheraton Hotel

EXHIBIT:

Nomenclature Committee

Joseph B. Wolffe, M.D., Chairman

TENTATIVE CLASSIFICATION OF ARTERIOPATHIES

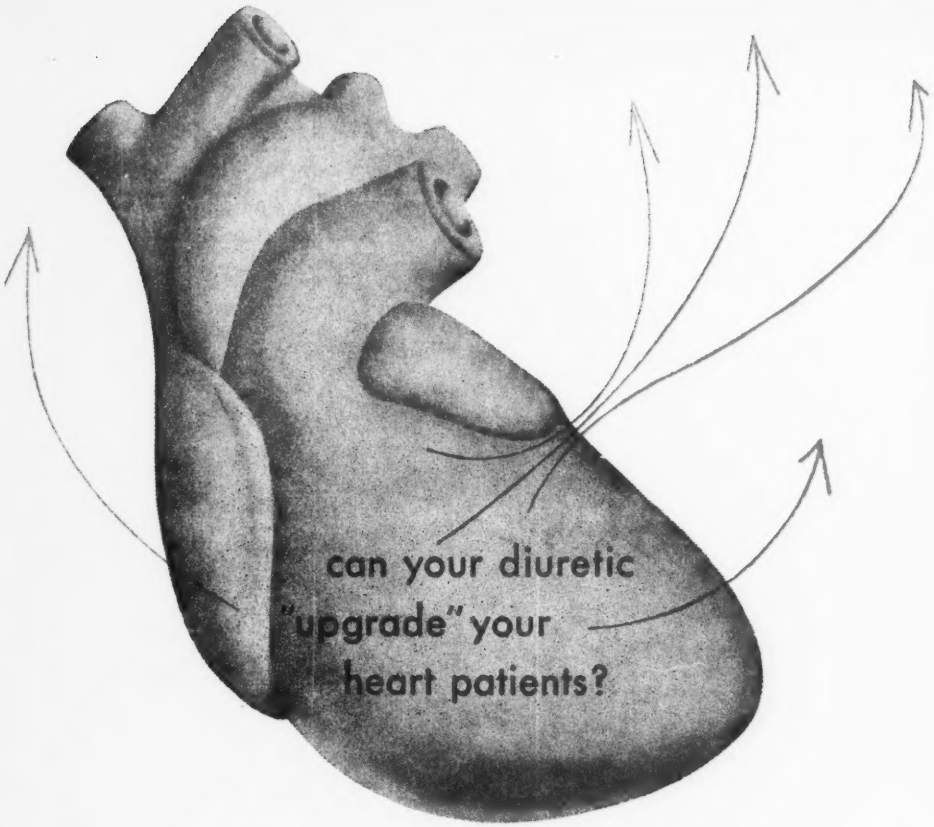
Registration Foyer
Sheraton Hotel

LUNCHEONS:

Sunday, November 5
12:00 Noon

Sheraton Hotel

Monday, November 6
12:00 Noon



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